VOLUME 100 • DE IBER 1957 • NUMBER 6

A.M.A. ARCHIVES OF

INTERNAL MEDICINE

INDEX NUMBER

The High-Pork Diet of the Negro of the Southern United States
G. E. Burch, J. R. Phillips Jr., and William Wood

The Search for an Experimental Counterpart of Pernicious Anemia
Maxwell M. Wintrobe

Megaloblastic Anemia in "Alcoholic" Cirrhosis
Sheldon E. Krasnow, John R. Walsh, Hyman J. Zimmerman, and Paul Heller

Digitalis Intoxication
Morton W. Shrager

Traumatic Involvement of the Thoracic Aorta
William F. Mazzitello

Diabetic Neuropathy: Pitfalls in Diagnosis
Max Ellenberg

Auricular Fibrillation
William L. Gould

The Sensitivity of Two Hundred Strains of Hemolytic Staphylococcus to a Series of Antibiotics
Robert G. Petersdorf, James A. Curtin, and Ivan L. Bennett Jr.

Uropepsin Excretion
Solomon J. Rosenberg

Ardmore Disease
William L. Wilson, Charles D. Williams, Saul L. Sanders, and R. P. Warner

The Use of Radioactive Fat in the Study of Absorption in Various Disease States
Donald Berkowitz and David Sklaroff

The Prevention of Myocardial Infarction
Benjamin Manchester

The Pulmonary Obstruction Syndrome in Schistosoma Mansoni Pulmonary Endarteritis
Ernesto J. Marchand, Raúl A. Marcial-Rojas, Roberto Rodríguez, Gerardo Polanco, and R. S. Díaz-Rivera

Hirsutism
William H. Perloff, Harry E. Hadd, Bertram J. Channick, and John H. Nodine

Vitamin K Deficiency Associated with Prolonged Antibiotic Administration
Halcott T. Haden

Atrial Flutter with 1:1 A-V Conduction
Jack Marks

Thyrotoxicosis Simulating Hyperparathyroidism
R. A. Pribek and R. C. Meade

Review of Neuropsychiatry
Stanley Cobb

Rudolph Virchow and Scientific Medicine
L. J. Rather

Books

News and Comment

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TABLE OF CONTENTS

VOLUME 100 DECEMBER 1957 NUMBER 6

EDITORIALS

PAGE

The High-Pork Diet of the Negro of the Southern United States
G. E. Burch, M.D.; J. H. Phillips Jr., M.D., and William Wood, M.D., New Orleans 859

ORIGINAL ARTICLES

The Search for an Experimental Counterpart of Pernicious Anemia
Maxwell M. Wintrobe, M.D., Salt Lake City 862

Megaloblastic Anemia in "Alcoholic" Cirrhosis
Sheldon E. Krasnow, M.D., Chicago; John R. Walsh, M.D., Omaha; Hyman J. Zimmerman, M.D., and Paul Heller, M.D., Chicago 870

Digitalis Intoxication
Morton W. Shrager, M.D., Philadelphia 881

Traumatic Involvement of the Thoracic Aorta
William F. Mazzitello, M.D., St. Paul 894

Diabetic Neuropathy: Pitfalls in Diagnosis
Max Ellenberg, M.D., New York 906

Auricular Fibrillation
William L. Gould, M.D., Albany, N. Y. 916

The Sensitivity of Two Hundred Strains of Hemolytic Staphylococcus to a Series of Antibiotics
Robert G. Petersdorf, M.D.; James A. Curtin, M.D., and Ivan L. Bennett Jr., M.D., Baltimore 927

Uropepsin Excretion
Solomon J. Rosenberg, M.D., Louisville 937

Ardmore Disease
William L. Wilson, M.D., Philadelphia; Charles D. Williams, M.D., Charlotte, N. C.; Capt. Saul L. Sanders (MC), U. S. A. F., and R. P. Warner, M.D., New York 943

The Use of Radioactive Fat in the Study of Absorption in Various Disease States
Donald Berkowitz, M.D., and David Sklaroff, M.D., Philadelphia 951

The Prevention of Myocardial Infarction
Benjamin Manchester, M.D., Washington, D. C. 959

The Pulmonary Obstruction Syndrome in Schistosoma Mansoni Pulmonary Endarteritis
Ernesto J. Marchand, M.D.; Raúl A. Marcial-Rojas, M.D.; Roberto Rodríguez, M.D.; Gerardo Polanco, M.D., and R. S. Díaz-Rivera, M.D., San Juan, P. R. 965

Hirsutism
William H. Perloff, M.D.; Harry E. Hadd, M.A.; Bertram J. Channick, M.D., and John H. Nodine, M.D., Philadelphia 981

Vitamin K Deficiency Associated with Prolonged Antibiotic Administration
Halcott T. Haden, M.D., Atlanta 986

Atrial Flutter with 1:1 A-V Conduction
Jack Marks, M.D., Columbus, Ohio 989

Thyrotoxicosis Simulating Hyperparathyroidism
R. A. Pribek, M.D., and R. C. Meade, M.D., Wood, Wis. 994

REVIEWS IN INTERNAL MEDICINE

Review of Neuropsychiatry
Stanley Cobb, M.D., D.Sc., Cambridge, Mass. 998

EVOLUTION OF MODERN MEDICINE

Rudolph Virchow and Scientific Medicine
L. J. Rather, M.D., San Francisco 1007

BOOKS

Reviews by Dr. William B. Bean and Others 1015

REGULAR DEPARTMENTS

News and Comment 1024

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VOLUME 100 DECEMBER 1957 NUMBER 6

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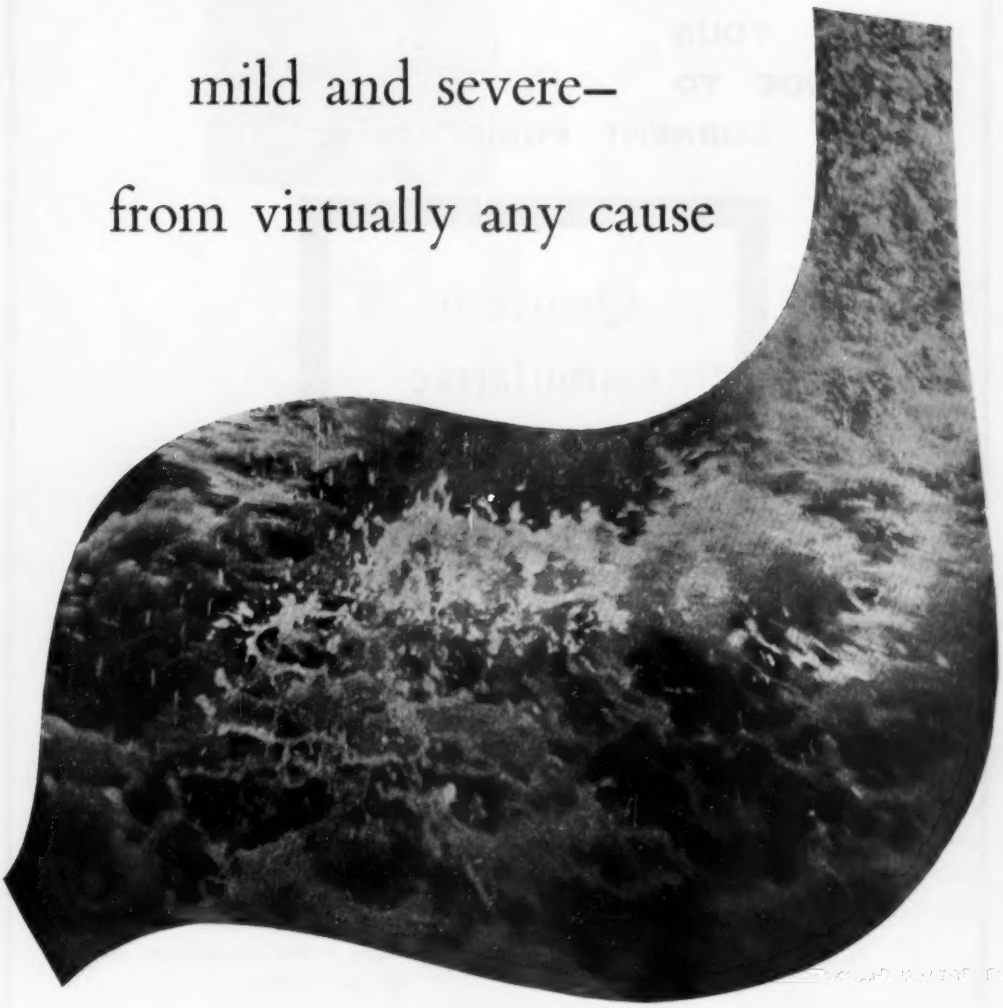

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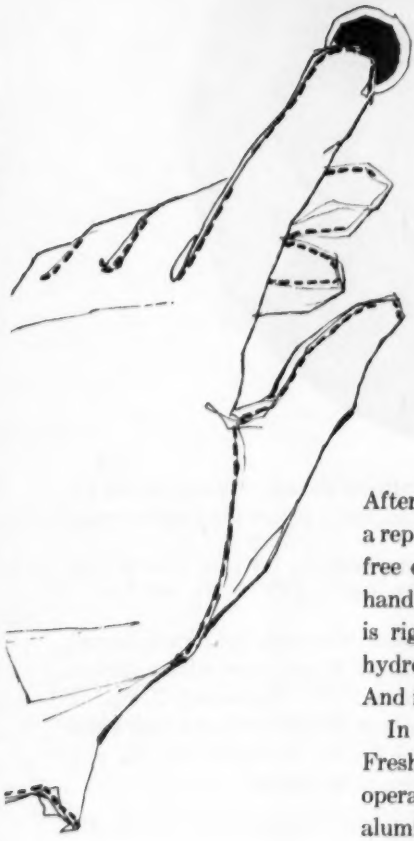

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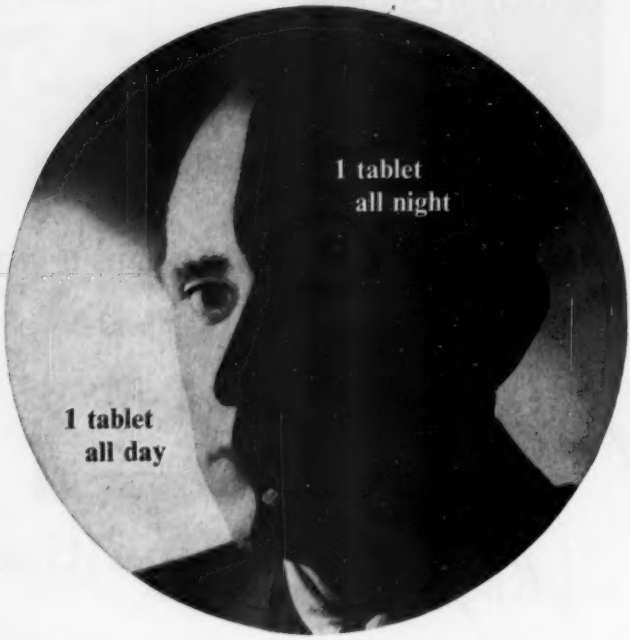

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[1]Fuller, H. L. and Kassel, L. E.: Antibiotic Medicine and Clinical Therapy, 3:322, October 1956.

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		†Coffee with cream and sugar

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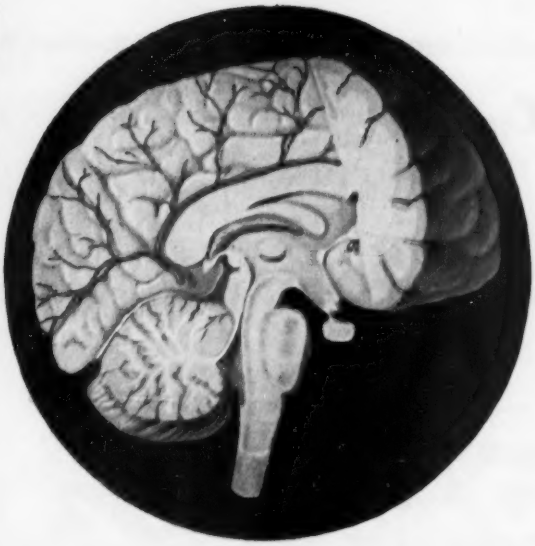

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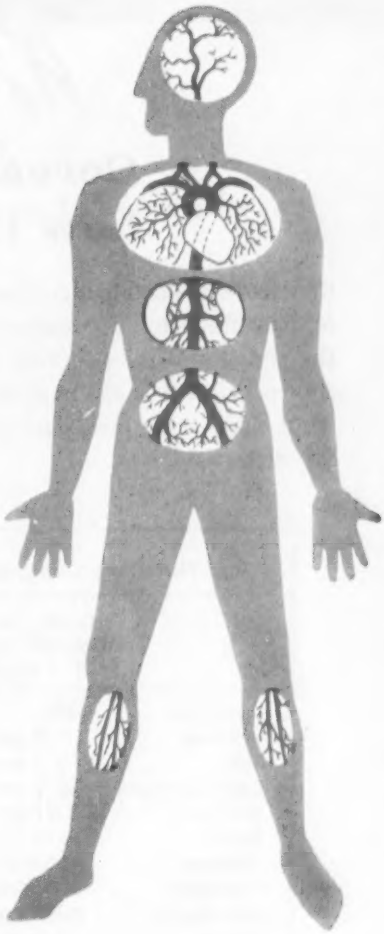

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Fat	5.3 gm.	0.6 gm.	4.7 gm.*	
Carbohydrate	32.2 gm.	22 gm.	6.0 gm.	4.2 gm.
Calcium	0.169 gm.	0.025 gm.	0.144 gm.	
Iron	1.5 mg.	1.4 mg.	0.1 mg.	
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Thiamine	0.16 mg.	0.12 mg.	0.04 mg.	
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Bowes, A. deP., and Church, C. F.: Food Values of Portions Commonly Used. 8th ed. Philadelphia: A. deP. Bowes, 1956.
Cereal Institute, Inc.: The Nutritional Contribution of Breakfast Cereals. Chicago: Cereal Institute, Inc., 1956.
Hayes, O. B., and Rose, G. K.: Supplementary Food Composition Table. J. Am. Dietet. A. 33:26, 1957.

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A.M.A. ARCHIVES OF
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Editorials

The High-Pork Diet of the Negro of the Southern United States

Recent interest in the relation of the consumption of fat to atherosclerosis has recalled an observation made many years ago of an interesting dietary peculiarity of the Negro of the southern United States, i. e., his extremely high intake of pork and pork products. Dietary factors among peoples of different races and geographic locations have often been incriminated as a cause for variations in racial distribution of certain diseases. Of particular interest is the appreciably higher incidence of hypertension in the Negro than in the white man of the southern United States and the greater frequency of hypertension, arteriosclerosis, and cardiovascular disease, in general, in the North American than in the African Negro.[1-11] Definite etiologic relations between diet and these diseases have not yet been unequivocally established, but circumstantial evidence can be offered.

The pork-eating habit of the Negro was evaluated by interviewing patients on the wards and in the clinics of the Charity Hospital concerning their consumption of pork and their clinical reaction to it. Our purpose was to obtain a general impression of the amount of pork included in the diet of the average Negro of the southern United States, of which the Negro population of Charity Hospital represents a sample. Without regard for diagnosis, several hundred white and Negro patients of both sexes were questioned by several physicians and medical students responsible for their care. The last 100 Negroes interviewed constitute the basis for these observations, which were essentially consistent throughout the entire series of patients interviewed. Included in this group of 100 were 30 men and 70 women, ranging in age from 12 to 85 years (mean, 53.9 years).

Practically all the patients ate fairly substantial servings of pork prepared in numerous ways several times each week, the maximal number of weekly servings being 45 (mean, 11.5 weekly). Pork used only for seasoning of other food was not considered as a serving. Three of these one hundred patients had rarely eaten pork in recent years, although it had been included in their diet previously. Most of these Negroes had eaten even larger quantities of pork earlier in their life but had probably reduced the intake as a result of the recent publicity against dietary fats, as well as their increased income, which permitted the procurement of costlier meats.

About 35% of these Negroes had symptoms that they attributed to the ingestion of pork. These included, in descending order of frequency, dizziness, nausea,

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eructation, vomiting, headache, indigestion, flatulence, blurred vision, diarrhea, heavy or full feeling in the head, faintness, scotoma, increased lacrimation, "boiling in the chest," general malaise, "hotness," weakness, epigastric burning, and epigastric fullness. The women had more disturbing symptoms than the men. Although the symptoms noted did not invariably occur every time each patient ingested pork, their occurrence was sufficiently frequent and severe to suggest strongly some association between pork and the appearance of symptoms.

Because of such unfavorable reactions, some of the subjects tried to avoid or reduce their intake of pork in later life. Of particular interest, however, was the continued ingestion of this meat by many patients in this study despite their anticipation, with fairly reliable accuracy, of these disagreeable symptoms. The Negro is aware that he relishes and eats a great deal of pork and often volunteers the information that it is not good for him, an opinion derived from his elders and physicians.

The factor in pork responsible for the symptoms remains to be identified. The high incidence of symptoms would seem to exclude a mechanism of allergy or hypersensitivity and to suggest the response to a substance that is metabolically disturbing. The responsible substance is probably not fat alone, since symptoms appeared when only lean pork was ingested. In considering the mechanism of the dyspepsia, one should realize that disease of the biliary tract, except for infectious hepatitis, is not as frequent in the Negro as in the white race.

It would appear, at least from the medical literature, that the African Negro consumes considerably less pork than the Negro of the southern United States. The significance of this difference in the production of certain cardiovascular disease states in these two groups of Negroes remains to be established. If pork increases the animal fat in the diet to a considerable extent, it is also interesting that the Negro has less coronary disease than the white man.[1-11] On the other hand, the American Negro has more hypertensive disease than the American white man but apparently not more arteriosclerosis. Pork does acutely disturb his health. A more extensive analysis of the relation between the ingestion of pork and the incidence of hypertension and other disease states in the Negro of the southern United States would provide an interesting, and perhaps enlightening, study.

G. E. Burch, M.D.
Department of Medicine, Tulane University School of Medicine, and Charity Hospital of Louisiana, New Orleans
J. H. Phillips Jr., M.D.
Public Health Service National Heart Institute Research Fellow, Department of Medicine, Tulane University School of Medicine, New Orleans
William Wood, M.D.
Public Health Service National Heart Institute Trainee, Department of Medicine, Tulane University School of Medicine, New Orleans

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The Search for an Experimental Counterpart of Pernicious Anemia

The George Minot Lecture

MAXWELL M. WINTROBE, M.D., Salt Lake City

I find it a particularly pleasant opportunity to give this, the seventh Minot Lecture because George R. Minot's Nobel Prize-winning discovery of the value of liver therapy in pernicious anemia was announced as my own career in medicine began and did much to shape my interests and course. As an intern, in 1925-1926, I observed the dramatic effect of this discovery on the lives and well-being of patients on our wards who but a few weeks before seemed to be doomed to inevitable death. Furthermore, later as an instructor at The Johns Hopkins Hospital attempting to delve into some of the problems of hematology, I found Dr. Minot's occasional visits stimulating and his little notes of encouragement when some paper of mine appeared in print genuinely inspiring. To Minot, the inquisitive student of disease, who worked with dogged determination in spite of his own ill health, to the biologist whose unsatiable curiosity brought so much to mankind, I therefore owe not only respect but genuine personal gratitude.

Many of the outstanding characteristics of George Minot as well as his most noteworthy contributions were described by his associate, William B. Castle, in the first Minot Lecture [1] and have been discussed in a most interesting fashion by Dr. Francis Rackemann in the book "The Inquisitive Physician," [2] and so I shall say no more here about Minot but will describe instead the merry chase he sent me on and what came thereof. In addition it will be profitable to review some of our present knowledge of pernicious anemia and to consider what questions remain to be solved.

That dietary factors play an important role in erythropoiesis had been proved by Whipple and then, more dramatically, by Minot and Murphy. A few years later Castle showed how the patient with pernicious anemia essentially starves "in the midst of plenty"; that is, he demonstrated how the patient with this disease is unable to absorb the dietary "extrinsic factor" because of the lack of an "intrinsic factor" which is normally produced by the stomach. These investigations pointed the way for an experimental approach to pernicious anemia. One could attempt to reproduce this disease by preventing the formation of intrinsic factor, as by gastrectomy, or one might observe the effects of the removal from the diet of various dietary essentials.

However, attempts by others, as well as by ourselves,[3] with certain rare exceptions had failed to produce macrocytic anemia by means of gastrectomy in animals. Futhermore, up to that time of all the totally gastrectomized subjects reported in the world literature there were very few cases in which pernicious anemia had developed, even though these patients had survived three years or longer after the operation. Consequently, it was decided to embark on a systematic study of the effects of the various dietary components on hemopoiesis.

One cause for the failure of experiments undertaken up to this time seemed possibly to be the species of animal employed. The natural diets of most laboratory animals

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differ from that of man. It was with this thought in mind that we came to choose the pig as our subject, for, at least in dietary habits, this animal does not differ greatly from man. Furthermore, it was known that desiccated hog stomach is effective in the treatment of pernicious anemia, and we had also observed in the pig fetus morphologic changes in the blood which were similar to those encountered in pernicious anemia. It was decided to carry out the experiments on very young pigs, both because it was hoped that by feeding such animals deficient diets early in their lives they would acquire only a comparatively small store of antianemic principle in their tissues and also because their rapid growth would tax their reserves and would result in nutritional deficiency more readily than might be the case in full-grown animals.

As is so often the case with research, the results of years of painstaking labor can be summarized in reverse logarithmic proportion. This is certainly true of our own experiments. The plan of our experiments was to select a very simple diet which would be nutritionally adequate in all respects and then to observe the changes which might take place when a single substance was withheld from the dietary regimen. A purified casein, together with sucrose and lard, provided the necessary protein, carbohydrate, and fat, and this was supplemented by a specially designed mineral mixture containing iron, copper, and other essentials, as well as vitamins A and D and a source of the B-vitamins. The pig does not seem to require dietary ascorbic acid.

When these experiments were commenced only thiamine was available in crystalline form, and the remainder of the B-complex had to be supplied in brewer's yeast. It was known at the time that autolyzed yeast is a source of "extrinsic factor" and could produce a hemopoietic response in pernicious anemia when given with normal gastric juice. Brewer's yeast, however, was considered to be inert either as extrinsic factor or when fed alone. It was a matter of surprise, therefore, when, in the course of testing in cases of pernicious anemia the hemopoietic potency of the various components of our experimental diet, it was observed that a good reticulocyte response and relief of the anemia followed the ingestion by our pernicious anemia patients of approximately 1.5 gm. of brewer's yeast per kilogram of body weight per day.[4] We now know as the result of the subsequent isolation of folic acid that this effect was not due to the action of the potent liver antianemic principle, cyanocobalamin (vitamin B_{12}), but was the result of the administration of conjugates of folic acid.

Later the various members of the vitamin B complex were identified and could be obtained in pure form, so that yeast was ultimately replaced by a mixture consisting of thiamin, riboflavin, nicotinic acid (niacin), pyridoxine, pantothenic acid, choline, inositol, *p*-aminobenzoic acid, folic acid, and cyanocobalamin.

Distinct and, in certain instances, very striking abnormalities result from deficiency of various dietary essentials. Here, however, attention will be paid mainly to the changes observed in the blood and in the nervous system, since these have a special interest in the present discussion. Before going further let me acknowledge the active association in these studies of Dr. George E. Cartwright since 1942.

Anemia resulting from nutritional deficiencies may be one of three types. Normocytic anemia, with normoblastic bone marrow, is observed in protein, lysine, or tryptophan deficiency, and when nicotinic acid, riboflavin, or pantothenic acid is lacking (Table 1). To date, dietary deficiency

TABLE 1.—*Normocytic Nutritional Deficiency Anemias in Swine* *

Deficiency	Leukopenia	Plasma Iron	Serum Copper	Erythrocyte Protoporphyrin
Protein	None	N	Low	N
Lysine	Present	N	N	
Tryptophan	Present	N	--	N
Nicotinic acid & protein	None	N	Low	N
Riboflavin	None	--	--	--
Pantothenic acid	None	--	--	--
Cyanocobalamin	None	--	--	--

* Bone marrow normoblastic. N signifies normal.

TABLE 2.—*Microcytic Hypochromic Anemias in Swine* *

Deficiency	Iron			Serum Copper
	Absorption	Plasma	Tissues	
Iron	Increased	Dec.	Dec.	N
Copper	Decreased	Dec.	Dec.	Dec.
Iron & copper	Decreased	Dec.	Dec.	Dec.
Pyridoxine	Increased	Inc.	Inc.	Dec.

* Bone marrow—normoblastic hyperplasia. N signifies normal.

of cyanocobalamin also has been associated only with the development of normocytic anemia, provided folic acid is furnished.[6] It is of interest to note, in passing, that leukopenia accompanies lysine or tryptophan deficiency.

Microcytic hypochromic anemia accompanied by normoblastic bone marrow hyperplasia develops when pyridoxine, iron, or copper is lacking (Table 2). It is noteworthy that in each of these circumstances there is a disturbance in iron metabolism. In iron-deficiency anemia this abnormality is a simple one, lack of sufficient iron to supply the needs. Such a deficiency results ultimately in a reduction in the number of circulating red corpuscles, and those that are formed are small and poorly filled with hemoglobin. It was rather surprising to find, however, that when pigs were fed a diet deficient only in copper and were given ample amounts of iron, a similar type of anemia developed and, as in iron deficiency, the content of iron in the serum was greatly reduced below normal.[7] Subsequent studies showed that absorption of iron is reduced in copper deficiency, and yet this is not the fundamental cause of the anemia, because iron administered intravenously does not prevent the development of this anemia.[8] There is, apparently, some fault in the utilization of iron in red cell formation. Possibly a copper enzyme is concerned in this step.

Deficiency of pyridoxine also results in microcytic hypochromic anemia, but here, in contrast to the iron- or copper-deficiency anemias, the serum iron is greatly increased above normal and the tissues are laden with deposited iron, giving a striking picture of hemosiderosis which only disappears when pyridoxine is administered.[9] It may be noted that this hemosiderosis does not develop if iron is withheld from the diet of pyridoxine-deficient animals.[10,11] Thus, in this situation at least, the body is unable to regulate iron absorption according to need, in contradiction to the widely held concept that there is an efficient intestinal mechanism which regulates iron absorption.

In pyridoxine-deficient swine a sharp fall in free erythrocyte protoporphyrin occurs at an early stage.[12] This just precedes the rise in plasma iron. This observation led us to suggest that pyridoxine may be concerned in the synthesis of protoporphyrin. Schulman and Richert [13] and Bogarad and Granick [14-16] now have evidence that pyridoxal-5-phosphate is required in the synthesis of δ-aminolevulinic acid, a precursor of protoporphyrin.

As might be expected, pyridoxine is involved also in a number of other metabolic processes. Thus a profound disturbance in tryptophan metabolism occurs when pyridoxine deficiency develops, epileptiform convulsions appear, and striking degenerative changes take place in the nervous system. These will be considered shortly.

We succeeded in producing macrocytic anemia experimentally only when a deficiency of folic acid was produced [17,18] (Table 3). As already stated, cyanocobalamin deficiency alone has not been accompanied by

TABLE 3.—*Macrocytic Nutritional Deficiencies in Swine* *

Deficiency	Anemia		Bone Marrow	Hemopoietic Response to		
	Severity	Type		PGA	Cyanocobalamin	PGA & Cyanocobalamin
PGA	++++	Macrocytic	Macronormoblastic	++++	0	++++
Cyanocobalamin	±	Normocytic	Normoblastic	0	±	±
PGA & Cyanocobalamin	++++	Macrocytic	Macronormoblastic few megaloblasts	+++	++	++++

* PGA signifies pteroylglutamic acid.

macrocytic anemia. The combination of folic acid and cyanocobalamin deficiencies, however, is associated with a more strikingly macrocytic anemia than that caused by folic acid deficiency alone.[19] Furthermore, although the bone marrow is hyperplastic in both instances, in the combined deficiency immature red cells were observed which more closely resembled pernicious-anemia megaloblasts than those seen in folic acid deficiency alone.

It is not generally appreciated to what lengths it is sometimes necessary to go in order to produce deficiencies experimentally. To produce folic acid deficiency, not only was folic acid omitted from the vitamin mixture and purified casein free of folic acid used, but a sulfonamide was given as well, in order to cut down growth of folic acid-producing bacteria in the bowel, which would otherwise supply the vitamin so carefully excluded from the diet. Even then the anemia which developed did not persist and spontaneous remissions occurred. Only by the administration of a folic acid antagonist could the anemia be maintained in continuing severity. Again, in the production of copper deficiency it was necessary not only to employ a copper-free diet with copper-free milk and iron, but even tap water could not be furnished the animals, since otherwise sufficient copper impurities became available to the animals to prevent the development of copper deficiency.

It is obvious that in these studies we were dealing with experimental animals, and it would not need to be pointed out that one cannot interpret animal experiments in terms of human disease without due consideration of all factors involved (Table 4) were it not for the fact that there are those who attempt to terrify the unwitting public and even mislead the sometimes unthinking medical profession into believing that the dangers of nutritional deficiency are ever present and that, in particular, all anemias should be treated with folic acid, cyanocobalamin and intrinsic factor concentrate, iron, copper, cobalt, and a number of additional substances thrown in for good measure. These proclaimers of doom and salesmen of the easy answer fail to recognize the protective mechanisms with which nature provides us. Thus, the requirements for certain substances are so low and their distribution in nature is so widespread that it is most difficult to escape them. Copper is an example. Storage in the body is another important protective mechanism. It has been postulated that the body requires at most 1μg. of cyanocobalamin per day,[20] and it has been estimated that 1000μg. to 2000μg. of this vitamin is stored in the body.[21] It follows, if this is true, that it would take at least two and a half to three years and possibly twice this long before the stored cyanocobalamin in the body was totally depleted in the face of no replenishment. Then again, it is likely that some of the vitamins produced by bacteria growing in the intestinal canal are absorbed and used.

The patient with pernicious anemia, however, does, in truth, starve in the midst of plenty. In spite of the generous provisions of nature he becomes deficient because he is unable to absorb the ample bounty about him. His is a "conditioned" deficiency which depends on his failure to absorb cyanocobalamin as the result of the absence of the gastric "intrinsic factor." But it needs to be emphasized that in the absence of special conditions which affect absorption of dietary substances and in the absence of excessive demands imposed on the organism, as by rapid growth, pregnancies, and excessive menstruation, deficiencies are unlikely to develop except when economic or other special circumstances impose on the person long-standing and severe dietary restrictions. In this country such restrictions are far less

TABLE 4.—*Factors Governing Development of Nutritional Deficiencies*

1. Requirement for substance in relation to its availability (compare iron and copper)
   Requirement may vary according to age and condition
2. Storage of essential substance
3. Bacterial synthesis
4. Factors leading to conditioned deficiency ("intrinsic factor", etc.)

common than the vitamin faddists would have us believe.

Returning briefly now to the experimental deficiencies in swine, attention may be directed to the nervous system. This is of special interest because of the combined system disease which is encountered in pernicious anemia. We were disappointed to find no evidence of spinal cord degeneration in folic acid-deficient or in cyanocobalamin-deficient swine. Neither did we encounter any sign of peripheral nerve degeneration in thiamine-deficient animals, in spite of the fact that this was long regarded as the "antineuritic vitamin." [22] On the other hand, extensive changes in the sensory neuron developed in pyridoxine-deficient and in pantothenic acid-deficient pigs, and such animals became ataxic and strikingly crippled by the neurologic defects.[23]

It will be seen, thus, that a number of aspects of the human disease, pernicious anemia, are simulated by certain of the deficiencies in swine. And yet it cannot be stated that a complete counterpart of the disease has been produced experimentally. How can this be explained?

It seems likely that the animals in which cyanocobalamin deficiency was produced did not at any time develop the degree of deficiency which occurs in pernicious anemia. In the presence of normal gastric mucosa and, presumably, normal secretion of intrinsic factor it is probable that sufficient cyanocobalamin is absorbed even from a deficient diet to prevent the development of severe anemia and degenerative changes in the nervous system. Yet it would be instructive to know whether the hematologic and neurologic manifestations of pernicious anemia would develop in experimental animals if the deficiency were severe enough. It is recognized that folic acid and cyanocobalamin are intimately related in blood formation. The details of this relationship are obscure. Will macrocytic anemia with megaloblastic bone marrow develop in spite of adequate supplies of folic acid when there is severe cyanocobalamin deficiency? This is not known, but I would venture to guess that it might not. It is interesting in this respect to observe that the hematologic relapses reported by Vilter et al.[24] in pernicious-anemia patients treated with folic acid and no liver extract or cyanocobalamin were apparently not accompanied by megaloblastic bone marrow. One wonders to what extent cyanocobalamin is actually related to the development of megaloblasts. Again, if the fundamental defect in pernicious anemia is an inability to absorb cyanocobalamin, why do these patients not absorb enough folic acid from their diets to prevent the development of megaloblastic macrocytic anemia? Is there some abnormality related to the absorption of folic acid or its utilization as well?

It has been suggested that both folic acid and cyanocobalamin are concerned in the synthesis of nucleoprotein and that folic acid is involved in deoxyribonucleic acid formation, whereas cyanocobalamin is concerned in the synthesis of ribose nucleic acid.[24,25] Deficiency of the latter, it is thought, affects especially the long axones of the nerve cells in the spinal cord. This may be true, but one wonders from our animal experiments whether pyridoxine or pantothenic acid is involved in some way as well. Furthermore, if the fundamental defect in pernicious anemia is the inability to absorb cyanocobalamin, why is not nervous-system degeneration rather than anemia the commoner manifestation of the disease?

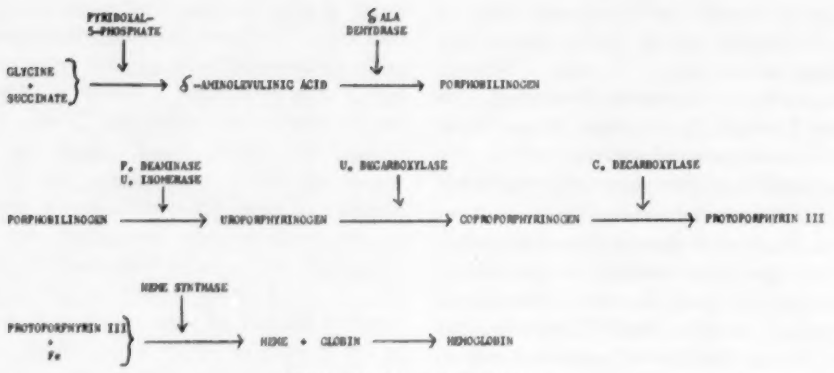
One means whereby it should be possible to produce a severer deficiency of cyanocobalamin than can be attained by dietary restriction alone is by total gastrectomy. We did, in fact, attempt the combination of total gastrectomy and cyanocobalamin deficiency in swine, but technical difficulties at the time forced us to abandon the attempt. That this approach should be fruitful is indicated by more recent experience with the late consequences of total gastrectomy in man.[26] It has been shown that following this procedure the serum cyanocobalamin level decreases, ultimately to levels found in

pernicious anemia, and then macrocytosis of the erythrocyte appears. These changes occur long before anemia develops. Although it sometimes occurs sooner, the average time required for the development of anemia in totally gastrectomized human subjects has been found to be four years after operation.

It may be asked, however, why should one be concerned with the experimental production of pernicious anemia if we already understand so much about this disease and can treat it so effectively? Those who have experience in research will answer that never has painstaking observation been made that it did not bear fruit, even though the result may not have been of the nature or even in the direction expected. It may be predicted that our present knowledge of the significance of cyanocobalamin in metabolism is but a fragment of what will be known ultimately, and it is possible that the additional knowledge will be of much broader significance than our limited imaginations permit us to guess. What is the importance of the impairment of cell division which is so characteristic of cyanocobalamin deficiency? What is its significance in relation to the development of carcinoma of the stomach in patients with pernicious anemia? What are the metabolic processes which are involved in the growth and development of the nervous system and what part do cyanocobalamin, pyridoxine, and pantothenic acid, in particular, play in this? Not even the surface of knowledge has been scratched in this respect.

It may be profitable, in closing, to call attention to some of the gains that have been made in our understanding of erythropoiesis as the consequence of the stimulus to research which the investigations of Whipple, Minot and Murphy, and Castle produced. We now know in large measure what substances are actually essential for the production of red corpuscles. We have also gained a dynamic concept of erythropoiesis and can visualize not only the morphologic consequences of deficiencies but also know where and at what rates the materials are used. It is noteworthy that, in many of the deficiencies we have discussed, both human and experimental, bone marrow hyperplasia rather than hypoplasia is found, in spite of the poverty of the circulating blood. Erythrokinetic studies, based largely on the use of radioactive iron, suggest that in the presence of these deficiencies shunts develop in the erythropoietic production line.[27,28] The great activity in the bone marrow which we can see is made largely ineffective because of the lack of some essential material, in the absence of which the synthetic process cannot be continued to its ultimate goal. Consequently, the products formed up to that point must be shunted off in other directions. One effect of this "log jam" is the hyperplastic bone marrow. Another is the large turnover of bile pigment which is seen in pernicious anemia. Much of this pigment is not derived from the destruction of red corpuscles but probably represents a shunting of unused materials consequent to failure of red cell synthesis.[29]

We are also beginning to learn a great deal about the biosynthesis of hemoglobin. Here may be mentioned the brilliant studies of Shemin and his co-workers, which have shown how porphobilinogen, the precursor of protoporphyrin, is formed from glycine and succinate. Others are studying the enzymes which serve the chemical reactions which take place (Figure). The finding that pyridoxal-5-phosphate is required in the synthesis of a precursor of porphobilinogen [13-16] has been mentioned already. Dr. H. C. Schwartz, in our laboratory, is engaged in the study of a factor, possibly an enzyme, "heme synthase," which is concerned in the insertion of iron into porphyrin to form heme; another member of our group, Dr. Harold Markowitz, has found a copper protein, erythrocuprein, in the red cell and is attempting to disclose its function. Investigators everywhere are busily involved in the pursuit of new problems opened up by attempts to solve older questions. Thus, if we may visualize as one unit the sum total of investigators



Biosynthesis of hemoglobin.

throughout the world who are engaged in the study of erythropoiesis, the little workshop in which Minot started has become an enormous and very busy and productive factory.

Summary

Among the substances known to be important in the production of red corpuscles are protein, iron, copper, pyridoxine, folic acid and cyanocobalamin (vitamin B_{12}). In experimental deficiencies in swine, pyridoxine and pantothenic acid have been shown to be necessary to maintain the integrity of the nervous system. Spinal cord degeneration from cyanocobalamin deficiency has not been produced experimentally, but it is clear from experience with pernicious anemia that this vitamin is important in maintaining the integrity of the nervous system.

In spite of the many highly significant studies concerning the pathogenesis of pernicious anemia which have been made in the past three decades, some questions still remained unanswered, and, in particular, there is need to study the factors which are concerned in the development of degenerative changes in the nervous system.

The stimulus to hematologic research which Minot's investigations provided has led to the development of additional knowledge not only concerning the substances required for erythropoiesis but also in regard to the kinetics of red cell production and the enzymatic reactions which are involved.

175 E. 21st South (5).

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Megaloblastic Anemia in "Alcoholic" Cirrhosis

SHELDON E. KRASNOW, M.D., Chicago; JOHN R. WALSH, M.D., Omaha; HYMAN J. ZIMMERMAN, M.D., and PAUL HELLER, M.D., Chicago

Introduction

Macrocytic anemia is common in patients with hepatic disease.[1-11] As early as 1883 an increase in the mean diameter of the erythrocyte was observed in "icterus catarrhalis."[12] There have been numerous references[1-11] to this phenomenon, but its mechanism remains incompletely understood. Most investigators agree that this macrocytosis is not caused by a deficiency of the "hematopoietic principle"[13] and is not associated with megaloblastosis of the bone marrow.[8,14,15]

The most frequent abnormality of erythropoiesis in cirrhosis of the liver is normoblastic hyperplasia.[8,14,15] It has been emphasized that this occurs even in the absence of bleeding and can be related to the shortened life span of the erythrocyte in this disease.[16] Occasionally "macronormoblasts"[8] as large as megaloblasts are present in the bone marrow of cirrhotic patients, but these cells otherwise have morphological features typical of normoblasts. Nevertheless, megaloblastic anemia in patients with cirrhosis has been described in several recent reports.[10,16-18]

This communication deals with seven additional patients with cirrhosis and severe megaloblastic anemia. During the period of observation of these seven patients many others with cirrhosis and anemia were studied. It therefore seemed of interest to consider the incidence of megaloblastic anemia in patients with cirrhosis and to attempt to correlate the clinical and laboratory features of these two abnormalities.

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From the Medical Services, Veterans' Administration West Side Hospital, Chicago, and Veterans' Administration Hospital, Omaha, and the Department of Medicine, University of Illinois College of Medicine.

PATIENT 1.—A 46-year-old white male bartender was admitted to the hospital because of severe weakness, swelling of the feet, shortness of breath, and a mild watery diarrhea. These symptoms started six weeks prior to admission and worsened progressively. The patient admitted to the consumption of approximately "one fifth" of whiskey per day for years. His diet allegedly consisted mainly of soups, bread, coffee, and occasional vegetable but very rarely of meat.

Physical examination revealed a slightly obese very pale man with a faint icteric tinge to the skin and sclerae. The blood pressure was 126/70; pulse, 120, and temperature, 98.6 F. The lungs seemed normal; the heart was slightly enlarged to the left. The heart sounds were normal, and no murmurs were heard. There was no ascites. The liver was palpable 9 cm. below the right costal arch in the midclavicular line. The spleen was not palpably enlarged. The genitals were normal. There was marked edema of the lower extremities. No neurologic abnormalities were found. On fundoscopy many pinpoint hemorrhages were seen. Proctoscopic examination revealed no abnormalities of the mucous membrane.

The erythrocyte count was 1,100,000 per cubic millimeter; the hematocrit, 13%, and the hemoglobin, 4.5 gm. per 100 ml. The white blood cell count was 11,500, with 74% polymorphonuclear leukocytes, 4% juvenile cells, 16% lymphocytes, 5% eosinophils, and 1% basophils. There were many hypersegmented polymorphonuclear leukocytes. The erythrocytes showed macrocytosis, anisocytosis, poikilocytosis. A few target cells were seen. The reticulocyte count was 0.8%. Specific gravity of the urine was 1.018; there was no proteinuria or glycosuria; the sediment was normal. Tests of hepatic functions showed minimal abnormality (Table 1, Patient 1). The initial electrophoretic analysis of the serum proteins showed a reduced value of albumin (37%) and increased values of all globulin fractions.

Nonprotein nitrogen, chloride, sodium, potassium, and carbon dioxide content of the blood was normal. The VDRL reaction for syphilis was negative. The Coombs test was negative. The gastric aspirate contained 69 units of free acid.

TABLE 1.—*Hepatic Function Tests*

Patient	Time	Bil., Direct/Total, Mg./100 Cc.	Sulfobromophthalein, %*	Alk. Phosph. Bodansky Units	Thymol Turb., Maclagan Units	Ceph. Floc.	Alb., Gm./100 Cc.	Glob., Gm./100 Cc.
1	On adm.	0.2/1.1	8.5	4.4	1.6	Neg.	3.7	1.8
	After 6 wk.	0.1/0.7	5.5	3.2	0.4	Neg.	4.1	2.5
2	On adm.	9.8/19	--	6.3	3.4	4+	3.2	2.9
				(Died after 2 wk.)				
3	On adm.	3.4/5.2	29	5.2	3.6	4+	3.2	2.7
	After 6 wk.	0.2/0.5	11	5.4	4.0	3+	4.7	2.6
4	On adm.	—/4.1	51.5	2.1	0.2	4+	2.2	1.9
				(Died after 2 days)				
5	On adm.	5.2/9.0	12	9.2	2.0	2+	2.8	2.7
	After 6 wk.	0.2/0.7	--	2.7	2.0	Neg.	4.7	2.3
6	On adm.	—/0.5	15.5	3.0	0.8	Neg.	3.3	3.4
	After 6 wk.	--	3.5	--	--	--	--	--
7	On adm.	1.1/3.0	16	7.7	3.2	Neg.	2.2	4.0
	After 6 wk.	--	13.0	8.6	1.8	--	3.5	3.4

* Retention in serum 45 minutes after injection of 5 mg. of dye per kilogram of body weight.

Stools did not contain blood, and fat was not demonstrated on staining with Sudan III. One determination of the 24-hour fat excretion in the stool yielded 5.4 gm. The serum iron level was 244μg. per 100 ml. (normal, 50 to 150). Oral glucose tolerance, measured by the two-hour test three weeks after admission, was normal. Measurement of absorption of radioactive cyanocobalamin (vitamin B_{12}) according to the method of Schilling[19] yielded normal results (24-hour urinary excretion 8.9%). Roentgenograms of the chest and gastrointestinal tract were normal. The electrocardiogram was normal.

Sternal marrow aspirate was markedly hypercellular, with predominantly megaloblastic erythropoiesis (Fig. 1*A*). The erythrocyte-myelocyte ratio was 2:1. Many large metamyelocytes with large and bizarre-shaped nuclei were present (Fig. 1*B*). The megakarycoytes were sparse and small, with diminished nuclear lobulation and no budding of platelets. The liver biopsy specimen revealed the changes of mild Laennec's cirrhosis (Fig. 1*C*).

After admission the patient received a transfusion of 1000 cc. of blood. His appetite improved rapidly, and the diarrhea subsided gradually. The hemoglobin values remained low despite absence

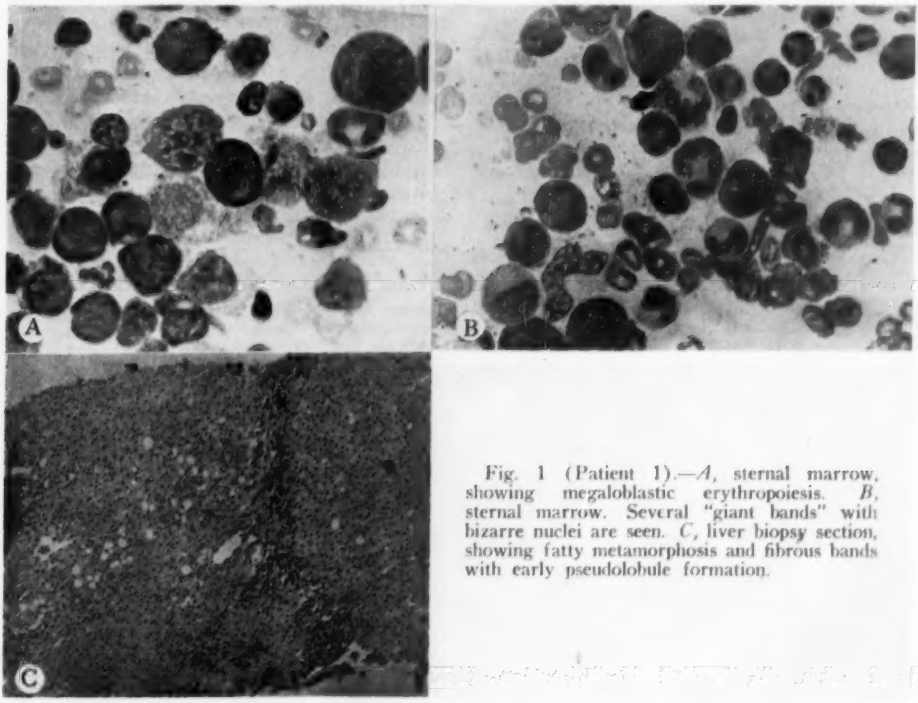


Fig. 1 (Patient 1).—*A*, sternal marrow, showing megaloblastic erythropoiesis. *B*, sternal marrow. Several "giant bands" with bizarre nuclei are seen. *C*, liver biopsy section, showing fatty metamorphosis and fibrous bands with early pseudolobule formation.

of bleeding. Two weeks after admission cyanocobalamin therapy was started, at a daily dose of 30μg. intramuscularly. Six days later the reticulocyte count reached the peak of 9%. As the hemoglobin and the erythrocyte levels rose, the reticulocyte count declined. Folic acid, added to this therapeutic regimen, did not lead to a second reticulocyte increase.

The erythrocyte count rose to 5,100,000 per cubic millimeter, and the hemoglobin, to 13 gm. per 100 ml. The serum iron level four weeks after admission was 81μg. per 100 ml. The bone marrow at that time was normal. Clinical improvement was rapid, but the size of the liver after two months of hospitalization had diminished only slightly.

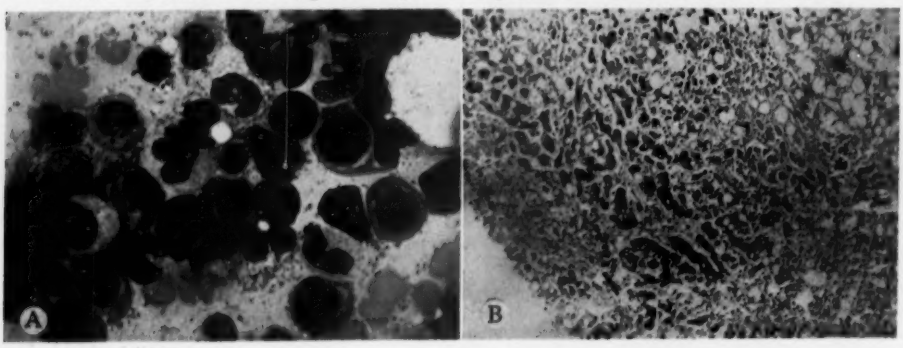
PATIENT 2.—A 37-year-old man entered the hospital because of pain and burning of the legs and feet for one and one-half years, anorexia and nausea for six months, and weight loss of 20 lb. in one year. He had had fullness for three months and a mild watery diarrhea for two weeks. He had been at another hospital twice during the preceding 18 months because of cirrhosis associated with jaundice and peripheral neuritis. He admitted to drinking a pint of whiskey a day for the previous 15 years.

Physical examination revealed a depressed moderately icteric white man with a coarse tremor of the hands. The temperature was 101 F; the pulse, 106, and the blood pressure, 124/80. The pharynx was injected. There were bilateral basilar moist and sibilant rales. The abdomen was distended, and a fluid wave was elicited. The liver descended 8 cm. below the right costal arch and had a firm and somewhat irregular surface. The spleen was not palpable. There was slight ankle edema. Neurological examination revealed normal results except for the "flapping tremor" of impending hepatic coma. Fetor hepaticus was noted, and there were numerous spider angiomata.

The hemoglobin was 7.9 gm. per 100 ml.; the erythrocyte count, 2,410,000 per cubic millimeter; the reticulocyte count, 2.6%; the leukocyte count, 5600 per cubic millimeter, with a normal distribution. There was marked macrocytosis, anisocytosis, and poikilocytosis. The sternal marrow showed markedly accelerated erythropoiesis, which was predominantly megaloblastic, and there were many large metamyelocytes with bizarre nuclei (Fig. 2*A*). The chest roentgenogram was normal. The VDRL reaction for syphilis was negative. The urine contained many leukocytes, some in clumps. There was a 2+ reaction for occult blood in the stool. The Sudan stain for fat was positive. The serum levels of nonprotein nitrogen, sodium, potassium, carbon dioxide, and chloride were normal. The serum bilirubin level was 19 mg. per 100 cc., one-half of which was direct bilirubin. The alkaline phosphatase was 6.3 Bodansky units; the cephalin flocculation, 4+; the thymol turbidity, 3.4 Maclagan units. The total protein was 6.1 gm. per 100 cc., with 2.9 gm. of globulin. An adequate 24-hour stool specimen contained only 7.36 mg. of urobilinogen.

After admission he remained critically ill, the jaundice became deeper, and the flapping tremor became more marked. When hepatic coma appeared imminent he received 100 mg. of hydrocortisone intravenously followed by 300 mg. of cortisone intramuscularly daily. There was little improvement, and three days later he developed colicky abdominal pain. At that time rebound tenderness of the markedly distended abdomen was found. After roentgenographic evidence of free air in the abdominal cavity was obtained the decision was made to subject the patient to laparotomy with use of local anesthesia. A large amount of ascitic fluid was drained, and a small perforation on the anterior wall of the duodenum was closed.

Fig. 2 (Patient 2).—*A*, sternal marrow, showing megaloblastic erythro- and granulocytopoiesis. Note the bizarre "giant bands." *B*, section of liver (autopsy specimen), showing Laennec's cirrhosis in the stage of fatty metamorphosis and necrosis (steatonecrosis).



Postoperatively coma deepened, shock developed, and the patient died two days later. The autopsy revealed peritonitis and severe hepatic cirrhosis, with necrosis and fatty metamorphosis (Fig. 2*B*). The gastric mucosa was not atrophic, and the small bowel, save for the duodenal ulcer, not abnormal to gross and microscopic examination.

PATIENT 3.—A 36-year-old white supply checker was admitted to the hospital because of severe weakness. He had been drinking "one fifth" of whiskey a day for several years prior to admission. During World War II he was wounded by a mortar shell, which wound was followed by chronic osteomyelitis of both legs. He was extremely weak, pale, jaundiced, confused, and disoriented. He had a fever of 101 F; pulse, 112, and blood pressure, 104/60. The mouth was edentulous, with several petechiae on the palate. There was a diastolic gallop and evidence of consolidation of the right middle lobe. The firm edge of a slightly tender liver was palpable 12 cm. below the costal margin. The left quadriceps muscle was markedly atrophic, and there were several draining irregular scars on the anterior surface of both legs. Spider angiomata were seen on the skin of the neck, trunk, and upper extremities. A "flapping tremor" was present, and the deep tendon reflexes were hyperactive bilaterally. Otherwise the neurologic examination was negative.

The erythrocyte count was 600,000 per cubic millimeter; the hematocrit, 8%, and the hemoglobin content, 2.3 gm. per 100 ml. There were 8400 leukocytes per cubic millimeter, with 77% polymorphonuclear neutrophils, 1% juvenile forms, and 22% lymphocytes. The platelets were normal. The bleeding time was four minutes, and the coagulation time, six minutes (Lee-White). The red blood cells showed macrocytosis, anisocytosis, targeting, and poikilocytosis. The white cells had toxic granulation. The bone marrow was megaloblastic, with numerous large bizarre metamyelocytes and juvenile neutrophils (Fig. 3*A*). The initial hepatic function tests are enumerated in Table 1 (Patient 3). Bilirubin was present in the urine.

The cardiolipin microflocculation test for syphilis was negative. Gastric analysis performed twice did not reveal any free acid after histamine injection. Determination of nonprotein nitrogen, CO_2 and electrolytes in the serum gave normal results. Cultures of the discharge from the wounds of the leg showed growth of Escherichia coli. Blood cultures were negative. The Schilling test revealed 9.8% of the test dose of radioactive cyanocobalamin excreted in the urine within 24 hours. A gastrointestinal series a few weeks after admission was normal. The stools had no increased fat content.

Because of the critical state of the patient he received 1000 cc. of blood. He also was given high doses of penicillin parenterally. The fever, which spiked to 104 F during the first three days after admission, subsided, and the patient's appetite improved. The jaundice disappeared gradually; the discharge from the leg wounds stopped. The anemia improved rapidly. The reticulocyte peak was only 7% ten days after admission, but the hemoglobin and erythrocyte count rose steadily. At the end of the eight weeks' hospitalization the hematocrit was 43% and the hemoglobin, 12.5 gm. per 100 ml. (Table 2). The bone marrow was normal. The changes in the results of the liver-function tests at this time are noted in Table 1. The needle biopsy of the liver, performed four weeks after admission, revealed only mild fatty metamorphosis (Fig. 3*B*). Except for the cyanocobalamin during the Schilling test the patient did not receive cyanocobalamin or folic acid during his entire hospital stay. He was discharged after two months' hospitalization.

PATIENT 4.—A 32-year-old white man was brought to the hospital because of mental confu-

Fig. 3 (Patient 3).—*A*, sternal marrow, showing megaloblastic erythro- and granulocytopoiesis. *B*, liver biopsy specimen, showing Laennec's cirrhosis with islands of fatty metamorphosis.

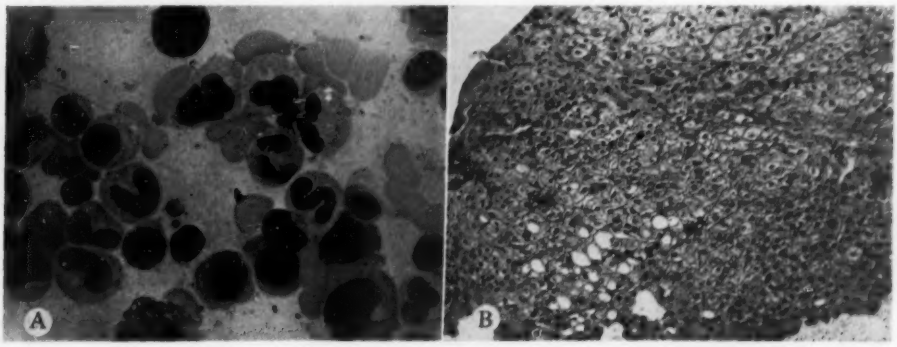


TABLE 2.—*Laboratory Data Pertinent to the Megaloblastic Anemia*

Patient	Hb. (Initial), Gm./100 Cc.	Reticulocytes		Hb. (After 6 Wk.) Gm./100 Cc.	Free Acid	Schilling Test, % *	Gastro-intestinal Series	Gluc. Tol.	Fecal Fat
		Initial	Maximum						
1	4.5	0.8	9	13	Present	8.9	Normal	Normal	Normal (quant.)
2	7.9	2.0	9	Died	(Duod. ulcer)				
3	2.3	0.8	7	12.5	Present	9.8	Normal		Normal
4	8.5			Died in 40 hr.					
5	8.5	0.8	20	13.5	Present		Normal	Normal	Normal
6	7.4	1.0		13.5	Present		Normal	Normal	Normal
7	7.5	1.6	6	14	Present	15.4	Normal	Normal	Normal

* Normal value: >3% of ingested dose of cyanocobalamin.

sion, jaundice, weakness, vomiting, and diarrhea. He was a severe alcoholic, who had been hospitalized with similar manifestations three times during the preceding three years. A liver biopsy performed two years prior to admission revealed the presence of Laennec's cirrhosis. Since his last discharge from the hospital he drank large quantities of whiskey daily until one week prior to admission, when the severity of his symptoms prevented the continuation of this habit.

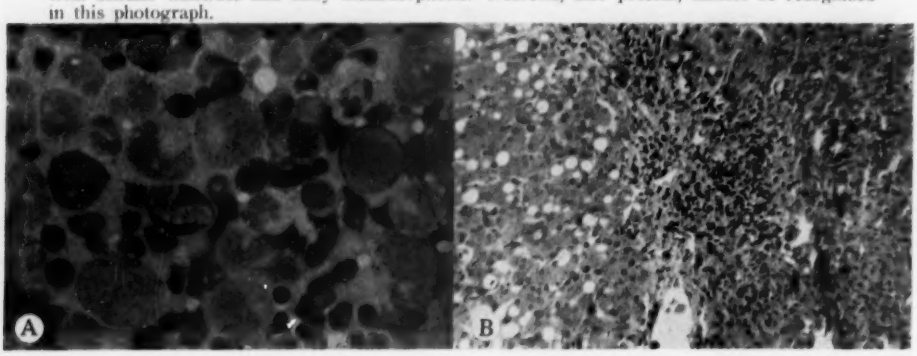
On admission he was found to be severely emaciated, pale, and slightly jaundiced. He was confused and restless. There was a marked fetor hepaticus. The blood pressure was 140/90; the pulse, 90. The heart tones were faint. The skin and sclerae were jaundiced, and there were numerous spider angiomata on the skin of the trunk, neck, and face. There were several petechiae on the skin of the lower extremities. Moderately severe ascites was present. The liver was palpable 5 cm. below the costal arch and was slightly tender. The spleen descended 5 cm. on deep inspiration. Tarry stool was found on rectal examination.

The hemoglobin was 8.5 gm. per 100 ml.; the hematocrit, 22%, and there were 2,900,000 erythrocytes. The leukocyte count was 5250 per cubic millimeter, 64% of which were polymorphonuclear leukocytes, 20% juveniles, and 16% lymphocytes. The specific gravity of the urine was 1008; glucose and protein were absent; the sediment contained many hyaline and granular casts. The cellular elements were stained with bile. In the serum were found 2.2 gm. per 100 cc. of albumin and 1.9 gm. of globulin. The sulfobromophthalein (Bromsulphalein) retention was 51.5% in 45 minutes; the cephalin flocculation, 4+; the thymol turbidity, 0.2 Maclagan units; the alkaline phosphatase, 2.1 Bodansky units. The bone marrow obtained by sternal puncture was very rich in spicules; marked megaloblastic erythropoiesis and large and bizarre metamyelocytes and juvenile neutrophils were present (Fig. 4*A*).

The patient failed to respond to treatment, and he died in hepatic coma 40 hours after admission. Although an autopsy was not obtained, permission was granted for postmortem needle biopsy of the liver, which revealed severe fatty cirrhosis (Fig. 4*B*).

PATIENT 5.—A 52-year-old unmarried laborer was admitted to the hospital because of severe weakness, jaundice, and diarrhea. He admittedly had subsisted on a diet consisting of wine, orange juice, and milk for several weeks. Because of vomiting and diarrhea he stopped taking milk and orange juice about two weeks prior to admission and ingested only wine. He had been an alcoholic

Fig. 4 (Patient 4).—*A*, sternal bone marrow; markedly hyperplastic, with megaloblasts and "giant bands." *B*, needle "biopsy" specimen of liver obtained after death, showing cirrhosis with cellular infiltrate and fatty metamorphosis. Necrosis, also present, cannot be recognized in this photograph.



for about 20 years and had not worked for about 14 months. He had lost 40 lb. of weight during the year prior to admission.

The patient was a cachectic white man, weighing 100 lb. The blood pressure was 90/70; the temperature, 97.2 F; the pulse rate, 110. He was very pale, and his sclerae were icteric. The tongue was heavily coated, and cheilitis was present. There was mild ascites. The liver was enlarged, especially the left lobe, which was palpable 15 cm. below the costal arch. The testicles were small. There was severe weakness of all extremities; the deep tendon reflexes were markedly hypoactive, and the skin and muscles of the feet and legs were tender. A minimal tremor of the hands and severe impairment of all modalities of peripheral sensory function was noted.

The red blood cell count was 2,500,000 per cubic millimeter; the hematocrit, 28%; the hemoglobin, 8.5 gm. per 100 ml., and the reticulocyte count, 0.8%. The erythrocytes showed anisocytosis, macrocytosis, poikilocytosis, and targeting. The white blood cell count was 6400, with 79% polymorphonuclear leukocytes, predominantly hypersegmented, 2% juveniles, and 19% lymphocytes. There was toxic granulation. The prothrombin, bleeding, and coagulation times were within normal limits. The platelet count was normal. The bone marrow showed increased predominantly megaloblastic erythropoiesis. There were numerous large metamyelocytes of the "perniciosa type." *

The VDRL reaction for syphilis was negative. Gastric analysis yielded free hydrochloric acid after histamine injection. The urinalysis revealed the presence of bilirubin and urobilinogen (two-hour Watson test, 7.5 Ehrlich units). There was no occult blood in the stool, and the number of fat droplets was not unusual. The fasting blood sugar, glucose tolerance, nonportein nitrogen, and electrolytes were within normal limits.

The hepatic function tests after admission are enumerated in Table 1 (Patient 5). The chest roentgenogram showed some rarefaction of pulmonary markings; the right diaphragm was slightly elevated. X-ray examination of the upper and lower gastrointestinal tract, including the small bowel and gall bladder, yielded normal results. The electrocardiogram was normal.

After an initial blood transfusion the patient received supplementary intravenous dextrose infusions with vitamin B complex. Daily intramuscular injections of cyanocobalamin, 30μg., were given. Within a few days the patient's appetite and strength improved, he stopped vomiting, and the paresthesia decreased. Thirteen days after initiation of cyanocobalamin therapy the reticulocyte count reached a peak of 20%, and 10 weeks after admission the characteristics of the erythrocytes, including the reticulocyte count, were normal (Table 2). The ascites and the jaundice gradually diminished, and liver function tests improved (Table 1, Patient 5). A liver biopsy two months after admission revealed Laennec's cirrhosis (Fig. 5).

The patient was discharged after three months of hospitalization. Several months later it was learned that he had resumed his alcoholic habits and had been admitted to a psychiatric hospital because of Korsakoff's psychosis.

PATIENT 6.—A 28-year-old single bartender suffered from burning pain and weakness of his legs and feet for one year prior to entry to the hospital. This was associated with a gradually increasing

* Slides were not available for photography.

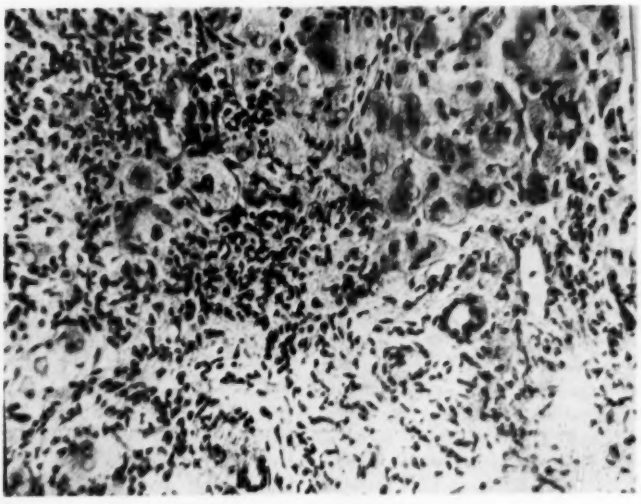


Fig. 5 (Patient 5).—Liver biopsy specimen, showing cirrhosis, necrosis, and cellular infiltration. Note hydropic nuclei of hepatic cells.

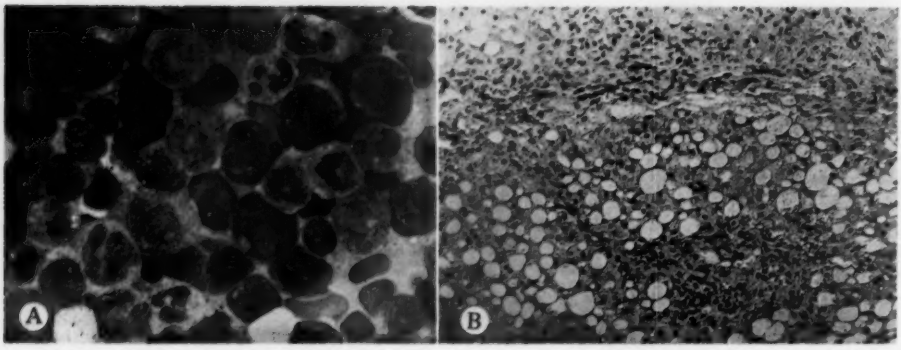


Fig. 6 (Patient 6).—*A*, sternal marrow, showing markedly hyperplastic marrow with megaloblastic erythro- and granulocytopoiesis. *B*, liver biopsy specimen, showing marked fatty metamorphosis and cirrhosis.

numbness and tingling of the legs, hands, and forearms. For two or three months he had experienced increasing shortness of breath on exertion and had been noticeably pale. There had been a gradual weight loss of 30 lb. in four or five years. For several years he had been frankly alcoholic, drinking about 8 to 12 bottles of beer and a pint of "Peppermint Schnaps" daily. His appetite had gradually diminished, and he vomited occasionally but never had hematemesis.

He was found to be poorly nourished and pale. Blood pressure was 130/84; the pulse, 130; the temperature, normal. Positive findings consisted of an enlarged liver, palpable 4 fingerbreadths below the costal margin, a barely palpable spleen, small soft testicles, and large areas of brownish discoloration of the skin of both ankles. The deep tendon reflexes were markedly hypoactive. There was severe hyperesthesia of the soles of both feet. The vibration sense and proprioception was diminished. Hyperesthesia of stocking-and-glove-like distribution was noted. Movements of the hands and fingers were clumsy.

The hepatic function tests are enumerated in Table 1 (Patient 6). Urinalysis showed normal results. The hemoglobin level was 7.4 gm. per 100 ml.; the erythrocyte count, 2,290,000 per cubic millimeter; hematocrit, 26%. The leukocyte count was 4500, with a normal differential. The platelet count, bleeding time, coagulation time, prothrombin time were normal. The reticulocyte count was 1%. The bone marrow showed megaloblastic erythroposiosis, with giant metamyelocytes and juvenile neutrophils (Fig. 6*A*). Fasting blood sugar and glucose tolerance were normal. Gastric analysis showed 51 units of free hydrochloric acid after histamine. There was no undigested material, including fat, in the stool. X-ray examination of the chest and upper and lower gastrointestinal tract showed normal results. Liver biopsy showed cirrhosis with fatty metamorphosis (Fig. 6*B*).

The patient responded rapidly to dietary measures, which included a high-caloric diet with supplementory vitamins. No folic acid or cyanocobalamin were administered. Six weeks after admission the hemoglobin and the red blood cell count were normal (Table 2).

PATIENT 7.—A 30-year-old butcher was admitted to the neurology service of the hospital because of progressive weakness of the lower extremities for two months. He had been a severe alcoholic for many years, with an average consumption of 1 qt. of gin daily. In addition he would drink 1 to 2 pt. of wine several times a week. He only had an occasional adequate meal. Except for one convulsive epidose, in 1954, he apparently was asymptomatic until two months prior to admission, when he started to have a feeling of tightness in both feet. This soon became associated with numbness and severe shooting pains in the thighs and legs. His gait had become unsteady, and he had had especially poor control of his left foot. During the two weeks prior to admission he had been unable to retain any food. He also had had increasing shortness of breath and had felt faint and dizzy. He had lost approximately 30 lb. in two months.

On admission he appeared exhausted and dyspneic. Tissue turgor was poor; the sclerae were icteric. The temperature was 100.6 F; the pulse, 120 per minute; the blood pressure, 106/65. There was a fetid odor of the breath; the teeth were in poor repair, and the gingiva, inflamed. The tongue was coated. The edge of the liver was palpable 8 cm. below the costal margin in the midclavicular line. It was smooth, firm, and slightly tender. The Romberg sign was present. Slight weakness of the right quadriceps muscle and severe weakness of the dorsal and plantar flexion of both feet were noted. The calf muscles and Achilles tendons of both legs were tender to compression. Pin prick and cotton perception were impaired over

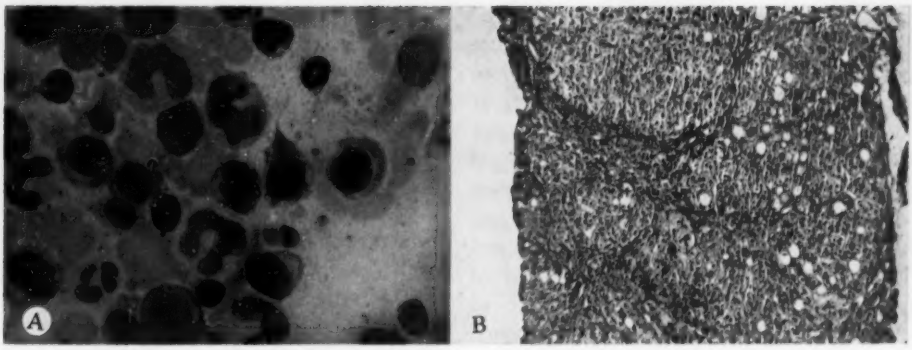


Fig. 7 (Patient 7).—*A*, sternal marrow, showing megaloblastic erythro- and granulocytopoiesis. Note the bizarre "giant bands." *B*, liver biopsy specimen, showing Laennec's cirrhosis.

the legs, feet, and toes. The vibratory sensation was also markedly diminished. There was slight awkwardness in the performance of the heel-to-knee test bilaterally. The biceps, triceps, and radial reflexes were hypoactive. The patellar and ankle reflexes were absent. There was no abnormal response to plantar stimulation, and the abdominal and cremasteric reflexes were absent. The position sense of the toes was only slightly disturbed.

The erythrocyte count was 2,900,000 per cubic millimeter. The hematocrit was 30%, and the hemoglobin, 7.5 gm. per 100 ml. There were 10,000 white blood cells per cubic millimeter, with 62% neutrophils, 34% lymphocytes, and 4% monocytes. On the stained smear the erythrocytes were predominantly macrocytic, with anisocytosis and targeting. There were many hypersegmented leukocytes. The reticulocyte count was 1.6%. The bone marrow was hypercellular and predominantly megaloblastic and there were numerous giant and bizarre metamyelocytes and juvenile neutrophils (Fig. 7*A*). The Schilling test revealed normal absorption of cyanocobalamin, with urinary excretion of 15.4% in 24 hours. On hemoglobin electrophoresis only hemoglobin A was found. The prothrombin time, bleeding time, and coagulation time were normal. The serum iron was 113μg. per 100 cu. cm. The urine examination revealed traces of albumin and bilirubin and a few granular casts. The VDRL test for syphilis was negative. Free hydrochloric acid was present in the gastric juice. The glucose tolerance test was normal. Roentgenograms of chest, esophagus, stomach, and small bowel were normal. The electroencephalogram and spinal fluid were normal. There was no occult blood in the stool. The liver biopsy specimen, obtained four weeks after admission showed Laennec's cirrhosis (Fig. 7*B*).

The patient's symptoms improved gradually, his appetite increased, and neurological function returned almost completely within one month. He gained weight on a high-protein high-caloric diet with supplement of vitamin B complex. No preparations containing folic acid or cyanocobalamin were given. The improvement of the results of the laboratory tests is noted in Table 1 and 2.

Comment

The seven cirrhotic patients of this report had megaloblastic anemia of varying severity. The bone marrow of all patients was hyperplastic, with predominantly megaloblastic erythropoiesis, according to classical criteria.[20,21] Granulocytopoiesis was characterized by the presence of a large number of giant bizarre juvenile neutrophils and metamyelocytes.

All patients were alcohol addicts, and in each the diagnosis of cirrhosis was confirmed by liver biopsy (six patients) or autopsy (one patient). The severity of the cirrhosis, however, varied greatly. In two patients the clinical illness was extremely severe, resulting in death (Patients 2 and 4). In three patients the degree of liver damage by clinical, functional, and histologic criteria was moderately severe (Patients 5, 6, and 7), and in two patients (Patients 1, and 3) the cirrhosis was considered to be mild. Jaundice was observed in three of the patients, while two others had only slight hyperbilirubinemia. The degree of sulfobromophthalein retention varied with the clinical severity of the liver disease. Hypoalbuminemia of vary-

ing degree was present in all seven patients. Two patients had slightly elevated serum globulin levels. In none was the thymol turbidity elevated. This is of interest, as hyperglobulinemia occurs frequently in cirrhosis, and the thymol turbidity is abnormal in 30% to 50% of patients with this disease.

Megaloblastic anemia in cirrhotic patients has also been reported by Jarrold and Vilter,[10] Movitt,[18] and Jandl.[16,17] Jarrold and Vilter described a small number of megaloblasts (less than 3%) and mentioned the absence of bizarre metamyelocytes in their three patients with cirrhosis and "megaloblastic maturation arrest." Movitt[18] has reported three cirrhotic patients with megaloblastic erythropoiesis and free hydrochloric acid in the gastric juice. Jandl,[16] in a study of 20 patients with hepatic cirrhosis and anemia, described 4 with megaloblastic anemia.

The seven patients of this report are additional examples of megaloblastic anemia in cirrhosis. During the period of this study (1953-1956), 350 persons with histologically proved cirrhosis were observed by us. In 96 of these patients the presence of moderately severe or severe anemia led to the examination of the bone marrow, which was found to be megaloblastic only in the seven described patients. This 7% incidence of megaloblastosis of the examined marrows represents 2% of the total number of cases of nutritional cirrhosis observed during the four-year period of study (Table 3).

Megaloblastic anemia in the patients of the present report could result from one or more of the following: (*a*) True Addisonian pernicious anemia could coexist with cirrhosis of the liver. (*b*) The megaloblastic anemia could be caused by the hepatic disease. (*c*) The severe dietary deficiencies of the alcoholic patient could, independently of the production of cirrhosis, have led to the development of megaloblastosis of the bone marrow. (*d*) Defective absorption of hematopoietic factors might result from the abnormal bowel function of cirrhotics.

TABLE 3.—*Incidence of Megaloblastic Anemia in Cirrhosis Proved by Biopsy*

	Patients, No.	%
Cirrhosis at biopsy	350	
Bone marrow examination	96	27.1
Megaloblastic anemia	7	2*

* 7.3% of examined bone marrows.

Intrinsic-factor deficiency has been indirectly excluded in five patients by the demonstration of free hydrochloric acid in the gastic juice. In three of these a normal pattern of absorption of radioactive cyanocobalamin was present. One additional patient died of a perforated duodenal ulcer complicating hepatic decompensation. He was presumed to have had at least normal gastric acidity. The seventh patient (Patient 4) died too soon after admission to the hospital for gastric acidity or intrinsic factor activity to be tested. This young severe alcoholic, during the two years that he was observed prior to his brief terminal illness, had no features to suggest the presence of pernicious anemia.

Could the megaloblastic anemia be the result of the cirrhosis? Studies of the ability of the cirrhotic liver to store erythropoietic maturation factor have yielded inconclusive results.[1,2,13,22] Cyanocobalamin is stored in the liver in a concentration of approximately 1μg. per gram of wet liver tissue.[23,24] Since the daily human requirement for this vitamin is approximately 1μg., it would take four to five years of dietary deficiency to deplete the liver stores. Quantitative measurements of the cyanocobalamin content of the cirrhotic liver have yielded markedly reduced values, but they have not been considered low enough to be responsible for the development of megaloblastic anemia.[23,24] Whether the increased cyanocobalamin serum level observed in cirrhotic patients[17,25-27] is related to impaired utilization of this factor or release from necrotic liver cells is unclear. Recently Jandl and Lear[17] concluded from their observations of four patients with cirrhosis and megaloblastic anemia that chronic alcoholism and cirrhosis might increase the requirement for folic

TABLE 4.—*Histologic Characteristics of the Hepatic Cirrhosis and Hemoglobin Values* *

Patient	Fibrosis	Fat	Necrobiosis	Hb.
1	1+	2+	0	4.5
2	4+	3+	+	7.9
3	±	1+	0	2.3
4	3+	4+	+	8.5
5	4+	1+	+	8.5
6	2+	3+	0	7.4
7	2+	2+	0	7.5

* Note lack of relationship between severity of anemia and severity of the hepatic disease.

acid, thus contributing to the development of folic acid deficiency. Nevertheless, were the megaloblastic anemia the result of the cirrhosis, a correlation might be expected between the severity of the liver disease and the occurrence of megaloblastic anemia. The severity, however, of the megaloblastic anemia bore no apparent relationship to the severity of the cirrhosis, which varied greatly in the seven patients of this study (Table 4). This lack of correlation is also reflected in the rarity of megaloblastosis in patients with severe and even fatal cirrhosis.

The possibility that the greatly deficient diet of many cirrhotic patients could result in clinical manifestation of deficiency of cyanocobalamin or folic acid has been considered.[16-18] As the diets of all seven patients had been grossly inadequate, an insufficient intake of these factors might have been responsible for the anemia. This situation would then resemble that described in food faddists, especially vegetarians,[25,28-31] who have developed megaloblastic anemia. Jandl and Lear,[17] however, were unable to demonstrate a greater dietary deficiency in the cirrhotics with megaloblastic anemia than in those who did not have megaloblastosis. Our experience has been similar. It is conceivable that marginal deficiencies of hematopoietic factors could become clinically manifest when erythropoiesis is accelerated as a result of hemolysis or hemorrhage. This mechanism possibly played a role in the pathogenesis of the anemia of one patient (Patient 4) of this study. Quantitative studies would be required to test the possibility that deficiency of cyanocobalamin or folic acid, whether absolute or conditioned, is responsible for the megaloblastic anemia.

Megaloblastic anemia has been shown to occur in a number of diseases characterized by defects of intestinal absorption. Absorption of glucose was normal in all five patients in whom an oral glucose tolerance test was performed. Fecal fat content was found to be normal in one patient by chemical analysis and in five other patients by microscopic examination of the stool. Radiographic studies, performed in five patients, revealed no abnormality of the small bowel. Cyanocobalamin absorption was normal in the three patients in whom the Schilling test was performed. Jandl and Lear [17] could not demonstrate any abnormality of folic acid absorption in their four patients. Thus the evidence at present does not implicate malabsorption as the cause of megaloblastic anemia in cirrhosis.

Three of the five surviving patients improved by dietary measures alone. In the two other patients the severity of the anemia made other measures mandatory. There was a prompt response to parenteral cyanocobalamin, but in one (Patient 1) of the two the reticulocyte peak was only 7%. When cyanocobalamin was supplemented with folic acid no further rise in the reticulocyte level occurred. Nevertheless, the anemia subsided completely, though gradually.

Megaloblastic anemia in cirrhosis is likely to be the result of several factors. Decreased ingestion, impaired absorption, increased requirement for cyanocobalamin or folic acid, or impaired utilization or storage of these substances may be acting variably and in combination to produce this infrequent complication of hepatic cirrhosis.

Summary

Seven alcoholic patients with hepatic cirrhosis and megaloblastic anemia are described.

Megaloblastic anemia was found to occur in 2% of 350 hospitalized patients with biopsy-proved cirrhosis.

The degree of the anemia could not be related to the severity of the cirrhosis.

The possible pathogenesis of the megaloblastic anemia in cirrhosis is discussed.

The late Dr. Karl Singer and Dr. Louis Limarzi gave valuable counsel in the evaluation of the patients, and the Medical Illustration Department, V. A. West Side Hospital did the excellent photomicrograph work.

Veterans' Administration West Side Hospital, 820 S. Damen Ave. (12) (Dr. Heller).

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Digitalis Intoxication

A Review and Report of Forty Cases, with Emphasis on Etiology

MORTON W. SHRAGER, M.D., Philadelphia

Several authors [1,2,6] have reported an increasing incidence of mild and severe disability in their cardiac patients associated with the use of digitalis preparations and presumably due in many instances to misuse of the drug—this despite abundant recent warnings in the literature about the increased hazard of rapid digitalization, the need for careful follow-up of patients who are being digitalized, with frequent readjustment of dosage, and the danger of free use of digitalis under certain limiting circumstances, the most notable being advanced and advancing congestive failure. It is commonly offered that the range between therapeutic and toxic doses is narrow, and this cannot be doubted. On the other hand, DeGraff [3] points out that many physicians give such a small dose that it is practically useless. "We must be sure that the patient has just enough digitalis, that he is neither underdigitalized nor toxic." The premise of this paper is that this is usually possible.

Method of Study

The charts of 112 patients admitted to the private and ward services of the Northern Division of the Albert Einstein Medical Center during the past five years (through 1952) with strong clinical suspicion of digitalis intoxication were reviewed. Forty of these, in which the diagnosis seemed well established, were selected and analyzed, especially with regard to the chemical and human factors which might have caused intoxication in each case. Cases were collected to reemphasize and occasionally to criticise certain recently reported concepts of the etiology of digitalis intoxication. Criteria of exclusion were adopted to select cases. These are listed in Table 1.

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TABLE 1.—*Criteria of Digitalis Toxicity Applied for the Screening of Doubtful Cases* *

A. Must be taking 50% or more of the average recommended dose [6,7]

B. Two or more of the following must also be present:

1. Strong clinical suspicion of digitalis intoxication based on signs or symptoms suggesting this syndrome to the attending staff
2. Return of signs or symptoms to normal after withdrawal of digitalis or reduction of dosage or potassium therapy, this change occurring within a period reasonably commensurate with the type of digitalis preparation being used
3. One of the following arrhythmias by ECG: paroxysmal auricular tachycardia with block, partial A-V dissociation ("interference dissociation"), runs of bigeminy or trigeminy due to frequent ventricular premature systoles
4. Good evidence of a predisposing factor, e. g., demonstrably low serum potassium level; I. V. Ca therapy; oliguria or massive diuresis

C. Not included for screening of cases as too nonspecific:

1. Ventricular extrasystoles; auricular extrasystoles, flutter, or fibrillation; 1st-, 2d-, or 3d-degree heart block; coupling due to auricular extrasystoles, etc.
2. Diuresis, unless massive and obviously related in time to the occurence of toxicity
3. Liver or kidney disease, unless accompanied by oliguria

* These criteria were derived while the study was in progress and reapplied to previously accepted cases. It is recognized that cases of toxicity may have been excluded. It was felt, however, that criteria of exclusion must be supplied to define what types of cases one is including as examples of "digitalis intoxication." Failure to include criteria for diagnosis caused some confusion in my mind as I was reading other reviews of this subject.

TABLE 2.—*Age Incidence of Cases of Digitalis Intoxication*

Age *	Intoxicated Group (40 Cases)		Control Group (40 Cases) †	
	No.	%	No.	%
70 or older	18	45	17	42
60 or older	31	77	29	73

* Average age in intoxicated group, 65; in control group, 66.
† Receiving therapeutic dosage of digitalis without toxicity.

TABLE 3.—*Relation of Severity of Cardiac Disease to the Cases of Digitalis Intoxication Reported Here*

Class *	Intoxicated Group (40 Cases)		Control Group (40 Cases)	
	No.	%	No.	%
IVd or IVe †	34	85	31	78
IIIc	2		8	
IIb	2		0	
Unknown	2		1	

* Classified according to the New York Heart Association.[14]
† These two categories could not be distinguished on the basis of information available on patient's charts.

Results

Age Incidence (Table 2).—Crouch, Herrmann, and Hejtmancik [2] point to an increased susceptibility to digitalis intoxication with advancing age but attribute this to progression of cardiac failure. DeGraff [3] and Kay [7] have also recommended cautious administration of smaller doses on a carefully individualized basis to the aged.

In this series the average age at which digitalis intoxication occurred was 65. Eighteen patients (45%) were 70 years of age or older; thirty-one patients (77%) were 60 years old or older. On the other hand, in an unselected series of 40 patients who were receiving therapeutic doses of digitalis but were not showing manifestations of toxicity the average age was 1 year older—66 years old. Seventeen patients (42%) in this control group were 70 years old or more, and twenty-nine patients (73%) were 60 years old or older. It seems then that age in itself did not preclude the use of therapeutic doses of digitalis.

Severity of Cardiac Disease (Table 3).—Many recent articles have underlined the fact that the margin between therapeutic and toxic doses of digitalis decreases with advanced and advancing heart disease. This interesting concept will be discussed at greater length below, when etiology of toxicity is considered. Table 3 reveals that the great majority of patients in this series were estimated by the attending staff or by the author to fit into Class IVd or IVe of the New York Heart Association [16] with regard to their cardiac status. However, 78% of 40 "controls" who were receiving digitalis without toxicity also fell into Class IVd or IVe Patients with advanced heart disease then can be given carefully controlled therapeutic doses of digitalis without toxicity, and, again, this is a major tenet of this paper. This is not to say, of course, that patients with severe myocardial disease are not toxicity-prone. Quite the opposite is true, as will be pointed out below. It is suggested, however, that intelligent dosage will usually prevent toxicity in this group of patients.

Type of Myocardial Disease Associated with Toxicity (Table 4).—In series by Flaxman [8] and by Crouch et al.[2] the distribution of types of cardiac lesions associated with digitalis intoxication was similar to the distribution of these lesions in the population group being sampled. Thus, hypertensive and arteriosclerotic heart disease head the list. The accompanying myocardial lesion in the present series, which is composed for the most part of elderly Jewish patients, was also felt to be nonsignificant when compared to nontoxic controls. There is neither support nor denial in this series for statements that acute myocardial infarction [2,3,7] and active rheumatic carditis [2] predispose to digitalis intoxication. Five cases, however, were associated with acute myocardial infarction, and in three of these, patients were

TABLE 4.—*Type of Myocardial Disease Associated with Toxicity*

Type of Heart Disease	Intoxicated Group (40 Cases)		Control Group (40 Cases)	
	No.	%	No.	%
Chronic arteriosclerotic	32	80	27	68
Hypertensive cardiovascular	20	50	10	25
Acute myocardial infarction	6	15	4	10
Rheumatic (all types)	6	15	5	12.5
Congenital	2	5	1	2.5
Pericarditis	0		1	2.5

TABLE 5.—*Comparison of Digitoxin and Digoxin with Regard to Severity of Toxicity and Occurrence of Nausea and Vomiting*

Total Treated	Digitoxin		Digoxin	
	No.	%	No.	%
Total treated	21		12	
Signs without symptoms	0		2	
"Moderately severe" or "severe" toxicity	19	90	8	67
"Mild" toxicity	2	10	5	33
Nausea and/or vomiting	14	67	10	83

intoxicated by doses which were not previously toxic to them during long periods of digitalis therapy (0.1 mg. digitoxin and 0.5 mg. digoxin daily).

Clinical Data (Table 5).—Most of the interest in this area has centered about three questions.

1. How often do signs of cardiotoxicity constitute the first clinical evidence of digitalis intoxication?

Crouch et al.[2] found in a review of 100 cases that 59% of patients had both signs and symptoms as the initial manifestations, 21% had signs alone without symptoms, and 20% had symptoms without signs. Cohen[9] reports that symptoms may be absent even in the face of profound disturbances of rhythm. It has been suggested[3] that early symptoms—especially anorexia—may be missed and that these become "masked" with continuing high dosage until toxicity develops. Moody[10] found 23 of 43 patients with digitalis intoxication presenting with signs only. Herrmann et al.[1] report 17 of 44 cases without symptoms. Flaxman[8] reports that 66.6% of 30 patients with toxicity due to digitoxin had no symptoms and that "signs of disorders of the cardiac mechanism, especially the more serious conduction disturbances, were the earliest and most frequent clinical and ECG manifestations in these (30) cases of digitoxin poisoning." Digitoxin has also been indicted by many other writers[2,9-11] in this respect. A relative paucity of gastrointestinal symptoms associated with its use is claimed.

More rigid criteria of selection assured that only a small percentage of the cases reported here (3 out of 40) presented signs of digitalis intoxication without symptoms. However, there is evidence of the potential danger of digitoxin in this regard (Table 5). Twenty-one of the forty patients (53%) were receiving digitoxin, and twelve (30%)

TABLE 6.—*Cases in Which Increasing Manifestations of Congestive Heart Failure Were Attributed to Digitalis Intoxication* *

Case	Age	Sex	Diagnoses	Signs & Symptoms at Time of Intoxication	ECG Changes	Digitoxin Dose, Mg.	Therapy & Effects
1	69	M	ASHD; old myoc. inf.; p. ed.; IVe	Symp. of p. ed.; vomit.; irreg. pulse	Aur. fib.; multifoc. multiform PVC; "marked dig. effects"	0.2 on 4 of 5 days; occas. inc. to 0.4	Stop dig. & oral KCl-NSR in 7 days with diuresis & improvement of failure
2	71	F	ASHD; HCVD; old inf.; CHF; IVd	Abd. pain; nausea & vomit.; green & yellow lights; bradyc. & prem. cont.; failure symp.	1st-deg. block; bradyc.; nodal esc.; PVC freq.	0.1 daily 1 yr.	Stop dig.; improved failure symp. & abd. pain
3	50	F	Chr. rt. ht. dis.; MI & MS; CHF; IVd	Abd. pain; N. & V.; inc. symp. CHF; 20 es. per min.	PVC; PAC	0.5 digoxin daily 2 yr.	Dec. dose to 0.25 mg. daily; less SOB, PVC, & Aur. es. in 3 days
4	48	M	Rt. ht. dis.; MS & MI; CHF; p. ed.; IVd	Inc. symp. CHF; bigeminy	Mult. PVC	0.2 b. i. d. 7 days (prev. maint. dose 0.2 daily); death 1 hr. after 0.4 lan. C 7th day	Patient died
5	82	F	ASHD; HCVD; p. ed.; IVe	Symp. fail.; palpations; many prem. cont.	Many A-V nodal prem. cont.; "marked dig. eff."	0.1 daily 3 yr.	Stop dig. 11 days; fewer es. & no recurrence attacks of p. ed., which were previously very frequent
6	65	F	ASHD; HCVD; old CVA; CHF; IVe	Failure symp.; n. & v.; abd. pain; scotomata; dim vision; headaches; wkness; bradycardia; irreg. pulse rate	Aur. fib.; freq. multif. PVC; bigeminy; "marked dig. effects"	0.2 daily for "years"; 0.4 for 3 days prior to toxicity	KCl & quin.; improvement of failure & dec. es. in 4 days

* ASHD indicates arteriosclerotic heart disease; p. ed., pulmonary edema; PVC, premature ventricular contractions; NSR, normal sinus rhythm; HCVD, hypertensive cardiovascular disease; CHF, congestive heart failure; esc., escape; MI, mitral insufficiency; MS, mitral stenosis; N. & V., nausea & vomiting; es., extrasystole; PAC, premature auricular contractions; SOB, shortness of breath; CVA, cerebrovascular accident.

TABLE 7.—*Over-All Incidence of Symptoms and Signs of Digitalis Intoxication in Forty Cases*

Symptoms and Signs	Cases	
	No.	%
Gastroenterological	29	73
Nausea and/or vomiting	26	65
Anorexia	12	30
Abdominal pain	9	22
Diarrhea	4	10
"Neurological"	19	48
Visual changes: blurring, scotomata, green & yellow flashes of light	6	15
Lethargy, weakness, malaise, somnolence	6	15
Disorientation	6	15
Headache	5	13
Vertigo	2	5
Aphasia	1	2.5
Depression	1	2.5
Irregular pulse	33	83
Auricular fibrillation	14	
Bigeminy	11	
Bradycardia (60 or less)	10	25
Occasional extrasystoles	4	10
Increasing signs or symptoms of heart failure	6	15

were receiving digoxin at the time of toxicity. Of the 21 cases of digitalis intoxication associated with digitoxin therapy, 90% (19) were classed as "moderately severe" or "severe." Only 14 (67%) of these sufferred nausea or vomiting. Of the 12 episodes associated with digoxin therapy, 8 (67%) were classed as "moderately severe" or "severe," and 10 patients of the 12 (83%) suffered nausea or vomiting. Nausea and vomiting are of course the most prominent subjective manifestations of digitalis intoxication (Table 7). Digitoxin then produced severer toxicity with less marked subjective manifestations than digoxin in this group of patients.

2. Can digitalis intoxication cause increased signs and symptoms of heart failure?

Kyser [12] suggests that digitalis intoxication should be considered as an additional cause of refractory heart failure. "In patients with severe forms of heart disease, the daily requirement for a maintenance dose of digitalis may decrease as the cardiac lesion progresses. Under these circumstances, a so-called normal dose may become toxic, leading to abnormal rhythms or increasing signs and symptoms of failure. All too often such a situation is interpreted as one requiring more digitalis."

In six cases in this series it was strongly suspected that digitalis intoxication was responsible for increased symptoms of failure which had not responded to increased doses of digitalis. The most important features of these six cases have been outlined and charted (Table 6). In five cases symptoms of failure improved when digitalis was stopped or decreased. In four of these five patients who improved, improvement was associated with return of a marked abberation of rhythm to normal sinus rhythm—auricular fibrillation in one case, very frequent premature ventricular systoles in two cases, and many A-V nodal premature contractions in the fourth. One patient died before appropriate therapy could be attempted.

No mystery need be attached to this concept. There is already considerable experimental basis for the belief that toxic doses of digitalis can further poison the failing heart.[6,15,17] In a symposium on digitalis intoxication,[3] Bishop suggests that when the etiology of bigeminy, or premature ventricular systoles associated with congestive heart failure, is obscure, digitalis should be temporarily discontinued. It is suggested also that patients in failure with extrasystoles of ventricular origin may occasionally benefit from procainamide (Pronestyl) without reducing the dose of digitalis. It is implied that one is thereby assured a maximum therapeutic benefit of the drug even though toxicity is superimposed. Lown and Levine [6] suggest that potassium be given to such patients. They feel that improvement following potassium therapy suggests that digitalis is at least partially responsible for the patient's symptoms. However, the wisdom of giving the antidote while continuing the poison may be questioned. The gravity of the syndrome of digitalis intoxication will be subsequently emphasized.

3. Which are the commoner signs and symptoms of digitalis intoxication, and which are the most reliable?

Many writers have attempted to alter Withering's original description of digitalis intoxication, with only minor success. The cases here described (Table 7) conform for the most part with those reported. Nausea

and/or vomiting are by far the most prominent symptoms which bring to mind the possibility of digitalis intoxication. They were recorded in 65% of cases here reported. Anorexia, on the other hand, though recorded in only 30% of cases, was often an early symptom and was doubtless present before and with nausea in many cases. It must be sought for. Abdominal pain was present in 22% of cases but could not be attributed to digitalis intoxication in many of these. Diarrhea was reported in 10% of cases.

Neurological symptoms were emphasized by Batterman and Gutner.[13] Their definition of "neurologic" includes a wide range of symptoms. Almost all of these were observed in the present series of patients (Table 7). They state that these symptoms may occur "regardless of degree of toxicity and in the absence of any other manifestations of intoxication . . . . Gastrointestinal complaints are only slightly more common." In the present series, "neurological" manifestations were noted in 19 patients (48%). In only five of these (12.5%) did they occur in the absence of other symptoms. A total of 27 "neurologic" symptoms were elicited in this series, as compared with 51 gastrointestinal symptoms. No instances of neuralgia of the mandibular nerve or of other peripheral nerves was recorded. Visual changes—blurring, scotomata, dim vision, diplopia, and green or yellow flashes of light—were noted in six patients (15%). It was not possible to relate these symptoms to type of drug or dosage.

Because of the more rigorous criteria employed, signs of intoxication were reported without symptoms in only 3 of the 40 cases. A marked irregularity of the pulse was noted clinically in 33 cases. An additional four patients manifested occasional extrasystoles; so that 37 patients in all, or 93%, were found to have pulse irregularities. Eleven of these manifested runs of coupled rhythm. Fourteen of the arrhythmias were found by ECG to be due to auricular fibrillation, but eleven of these manifested other arrhythmias as well. Bradycardia, defined as an apical pulse rate equal to or less than 60, was found in 10 patients (25%).

TABLE 8.—*Arrhythmias Associated with Digitalis Intoxication in Forty Cases*

	100 Cases by Crouch[2], %	Present Series	
		No.	%
Ventricular premature	65	23	57
"Frequent"		18	45
"Occasional"		5	12.5
Bigeminy	34	10	25
Trigeminy		1	2.5
Auricular fibrillation	19	14	35
Attributable to digitalis toxicity		3	7.5
First degree heart block	10	13	33
Second degree heart block	7	6	15
Complete heart block	14	4	10
Wenckebach phenomenon		2	5
Nodal rhythm		5	12.5
Premature auricular contractions	16	4	10
Flutter with varying block	4	3	7.5
Paroxysmal auricular tachycardia with block	7	1	2.5
Partial A-V dissociation	9	1	2.5
Ventricular tachycardia	13	1	2.5
Sinus tachycardia	16	2	5
Wandering pacemaker	3	2	5

ECG Changes.—Crouch et al.[2] found arrhythmias in 80% of 100 patients with severe digitalis intoxication. In this series only 2 patients of 40 escaped this complication, an incidence of 95%. The results are listed in Table 8, alongside the series of Crouch. A higher incidence of severe arrhythmias in their series may be attributable to severer heart disease or severer toxicity.

The incidence of auricular fibrillation requires further discussion. This arrhythmia was found in 14 patients (35%) in this series. DeGraff[3] has stated that "the development of auricular fibrillation in a patient formerly in normal sinus rhythm is an important toxic manifestation of digitalis." In this series only three cases of auricular fibrillation reverted to normal sinus rhythm with lowering of the digitalis dosage and might therefore be ascribed to digitalis toxicity. Moreover, in a nonselected control group of 40 nontoxic patients, 8 cases (20%) of auricular fibrillation were noted.

Bigeminal rhythm is said to be associated most commonly with rheumatic heart disease and especially with auricular fibrillation.[6] Of 10 patients reported here with ECG proof of bigeminy, 6 had associated auricular fibrillation. Only two, however, were

TABLE 9.—*Incidence of "Digitalis Effects" by ECG in Toxic and Nontoxic Cardiacs*

No.	Description	"Digitalis Effects" Present		
		No.	%	
36	Intoxicated group	35	97	("marked" in 7[19%])
40	Receiving digitalis but nontoxic	34	85	("marked" in 1[2.5%])
10	No digitalis, but in congestive heart failure	5	50	

associated with known rheumatic heart disease.

So-called "digitalis effects" were found in 97% of the intoxicated patients, but these changes were found to be nonspecific when compared to control series (Table 9), as noted by other authors.[1,6,9]

First-degree heart block was very common. Thirteen of sixteen patients in whom the P-R interval could be measured were found to have P-R intervals which were greater than or equal to 0.20 seconds. The average was 0.23 seconds in the toxic group, 0.19 seconds in a group of 40 patients who were nontoxic, and 0.17 seconds in a small group of patients (10) who were in congestive failure but were not receiving digitalis (Table 10).

Etiology of Toxicity

The reported increase in the incidence of digitalis intoxication has been widely attributed to widespread use of purified glycosides, both orally and parenterally and both slowly and rapidly. Digitoxin has especially been indicted because of claims of fewer warning gastrointestinal effects (q. v.) and because of its cumulative action and slow excretion.[8,9,11] It is recognized by all who make these statements, however, that it is not primarily the pharmacology of the purified glycosides but rather a poor understanding of their correct use which is at

TABLE 10.—*Average P-R Interval*

No.	Description	Average Interval, Sec.
15	Toxic	0.23
30	Receiving digitalis but nontoxic	0.19
10	Cong. failure but no digitalis	0.17

fault. The following classification of etiology (Table 11) is based therefore on the concept that human error in the use of digitalis preparations, regardless of their nature, and in the management of certain problems related to congestive failure is very largely responsible for the increased recent incidence of digitalis intoxication. It is an attempt to express correctable human errors in the management of these 40 patients which resulted in intoxication.

TABLE 11.—*A Classification of Etiology of Digitalis Intoxication Based on Analysis of Forty Cases* *

A. Overdose of digitalis: 28 cases (70%)
   I. Absolute overdose—dosage grossly high: 8 cases (20%)
      (*a*) Increase in dosage in an attempt to manage intractable heart failure: 3 cases (7.5%)
      (*b*) Gross error by patient in taking prescribed dose: 1 case
      (*c*) Errors in dosage or timing by the attending staff: 4 cases (10%) (too much digitalis too rapidly administered)
   II. Moderate overdosage—dosage larger than maximum recommended,† but should not cause intoxication in normal hearts in the absence of limiting conditions (q. v.): 7 cases (17.5%)
      (*a*) Increase in dosage in attempt to manage intractable failure: 4 cases (10%)
      (*b*) Errors in criteria of dosage: 3 cases (7.5%)
         1. Use of pulse rate in absence of auricular fibrillation or flutter: 1 case
         2. Empiric revision of dose by patient on basis of subjective improvement: 2 cases
   III. Relative overdosage—dose within recommended range † but nevertheless excessive for the patient and his associated physical and chemical status: 13 cases (32%)
      (*a*) Continuation of a relatively high maintenance dosage in an effort to control intractable failure: 2 cases (5%)
      (*b*) Failure to follow up patients frequently and readjust dosage during long-term treatment of patients with congestive failure: 9 patients (23%)

(*c*) Failure to readjust maintenance dosage downward during limiting circumstances other than advancing congestive heart failure: 2 cases (5%)

B. Poor myocardial status—an etiologic factor in 29 cases (73%)

C. Electrolyte imbalance: 8 cases (20%)
   I. Potassium deficit: 6 cases
      (*a*) Due to diuresis: 4 cases
      (*b*) Due to infusion of hypertonic saline or dextrose: 1 case
      (*c*) Due to vomiting or diarrhea: 1 case
   II. Calcium therapy: 2 cases

D. Limiting conditions: advanced congestive heart failure, electrolyte imbalance, myocardial infarction, pulmonary embolism, hypothyroidism, advanced renal disease with oliguria, and advanced liver disease; these factors should be mentioned when present in association with digitalis intoxication; progress in prophylaxis and treatment of intoxication, however, lies in an awareness of their significance in relation to other categories already mentioned; i. e., "moderate overdosage" and "relative overdosage"

* It is felt that this classification of digitalis intoxication will be of value to physicians in separating in their minds correctable from noncorrectable etiologic factors. Mistakes in therapy can perhaps better be evaluated and avoided with such a classification in mind. It is, of course, incomplete, based as it is on analysis of only 40 cases of intoxication.

A. Overdose of Digitalis.—Dosage of digitalis cannot be based on charts or tables or on a patient's size or weight, i. e., it must be individualized. Secondly, the maintenance dose cannot be rigidly fixed for a given patient for all time, i. e., it must be reevaluated. Thus, individualization and reevaluation of dosage are two very important concepts in considering the etiology of cases of digitalis intoxication.

Thirty-two of the forty cases here reported were considered by me to be preventable by the attending physicians, and twenty-eight of the thirty-two instances of toxicity were due largely to errors in dosage. Three categories of overdosage were suggested by the types of errors involved.

I. Absolute Overdosage: The dosage in these cases was grossly high and was felt to be largely responsible for the occurrence of toxicity.

Eight cases (20%) were in this category. Reasons for the excessive dosage included the following ones.

(*a*) Increase in dosage in an attempt to manage intractable heart failure (3 cases). This concept has already been discussed, but it warrants further comment here; for many cases in the present series (nine, 23%) were attributable to attempts to augment an already adequate or excessive maintenance dosage in a failing heart. McMichael [14] suggests that when digitalis fails to be of benefit the end-stage of cardiac failure has been reached. "In its presence, it is never wise to give digitalis." Presentation of experimental evidence for this statement is not germain to this paper, but it is to be found in studies of the effects of toxic doses of digitalis and of congestive failure itself on the myocardial potassium content.[6,15] On the other hand, many writers [3,7] state that it is necessary to go to the toxic point with digitalis to be sure of a maximum therapeutic effect in many instances. This implies a thorough familiarity and constant check of the patient clinically and by ECG for "minor" symptoms and signs, and, as DeGraff pointed out,[3] these minor symptoms may be missed until serious toxicity has developed. He suggests that digitalization to the toxic point is often necessary in patients with severe congestive failure and with auricular flutter, since the margin between therapeutic and toxic doses becomes very narrow in these cases. Again, however, frequent ECG's and careful observation are emphasized if this course of therapy is attempted. Kay [7] writes that toxic and therapeutic doses may overlap in severely ill patients so that the maximum therapeutic effect may be associated with minor toxicity; but most patients, he feels, are helped by doses well below the toxic range.

(*b*) Gross error by the patient in taking the prescribed dose of digitalis resulted in one case of toxicity reported here.

(*c*) Errors in dosage or timing. This type of digitalization was responsible for four cases of toxicity in this series (10%). Too much digitalis was given or the amount given was administered too rapidly without waiting for the full effect of the preceding dose. Kay[7] suggests that "if the series is large enough sooner or later rapid digitalization will result in disaster." Errors in rapid digitalization were not a common cause of intoxication in the present series, however (two cases, 5%).

II. Moderate Overdosage: In these cases the dose was larger than the maximum recommended by Lown and Levine[6] but would probably cause few cases of digitalis intoxication in normal hearts. It is felt that this classification has practical significance; for these are the patients in whom a small increase above recommended dosage resulted in toxicity because of poor myocardial status, limiting conditions, kidney disease, or electrolyte imbalance. Seven patients (17.5%) were in this category. In retrospect these cases were due to faulty judgement in the following two respects.

(*a*) Increase in dosage in attempt to manage intractable failure (4 cases). This has been discussed above. Four of the total of nine cases which were due to attempts to manage intractable failure were associated with only "moderate" increase in dosage.

(*b*) Errors in criteria of dosage resulted in toxicity in the remaining three cases in this category. One was associated with the use of the pulse rate as basis for the use of digitoxin in a patient who did not have auricular fibrillation. The other two cases were due to empiric revision of the patient's dose by the patient on the basis of subjective feelings of improvement.

III. Relative Overdosage: This most important category is composed of those cases of digitalis intoxication (13 in number, or 32% of this series) in which the dose ranged within the maximum recommended by Lown and Levine[6] but was nevertheless excessive for the patient and has associated physical and chemical status. It is here that individualization of dosage and reevaluation of dosage are most important. It is felt that the great majority of these cases were preventable by reduction of dosage. Where evaluation of this group was possible, three categories of human error presented themselves predominently.

(*a*) Deliberate continuation of a relatively high maintenance dosage in an effort to control intractable failure. Most patients in this class fell into groups Ia and IIa. Two of the nine were placed in this class.

(*b*) Failure to follow up patients frequently and readjust dosage during long-term treatment of patients with congestive heart failure. This group of nine patients (23% of the series) is felt to be the most important of the series. It has already been noted that with increasing severity of congestive heart failure the therapeutic and toxic doses of digitalis come closer and may overlap. One group of these patients then probably became intoxicated while being given a constant maintenance dosage because of a progressively failing myocardium. These patients became toxic because of poor follow-up care, with failure to pick up early and minor signs or symptoms of toxicity, and to alter correspondingly the dosage as failure became severer. Reevaluation was at fault.

A second group, however, consists of those in whom the maintenance dose was simply too high, even though it fell within the so-called "range" of dosage suggested by such writers as Kay[7] and Lown and Levine.[6] These writers were of course well aware of this. Kay,[7] for example, states that approximately one patient in three receiving 0.15 mg. of digitoxin per day will require subsequent revision in dosage, usually downward. Furthermore, it is pointed out that 0.2 mg. of digitoxin per day will digitalize most patients within three weeks. This would seem to be a dangerous maintenance dose then for many cardiacs, though not necessarily for most. Of the nine patients in this series in whom toxicity was attributed to relative overdosage, five were

receiving 0.2 mg. of digitoxin daily; two were receiving 0.5 mg. of digoxin daily; one was receiving 0.15 mg. of digitoxin daily; one was receiving 0.1 mg. of digitoxin daily.

(*c*) Failure to readjust maintenance dosage downward during limiting circumstances other than advancing congestive heart failure. This group will also be discussed below under limiting conditions, but two cases of digitalis intoxication associated with acute myocardial infarction are included here to emphasize that toxicity in these cases may often be prevented by readjustment of a maintenance dosage downward with the onset of the limiting circumstance. One of these two patients was receiving 0.1 mg. of digitoxin, the other, 0.5 mg. of digoxin, when the acute infarction occurred. Both had good evidence by the criteria established (q. v.) of digitalis intoxication, and signs and symptoms returned to normal with discontinuation of digitalis and appropriate therapy. In other cases of toxicity associated with limiting conditions the condition itself seemed to be the most easily correctable or avoidable factor in the etiology of intoxication. These cases were therefore classed below, although a reduction in dosage would obviously have prevented toxicity in these cases also. The other three of five cases of myocardial infarction here classified were also felt to be dosage problems and have already been so listed (Classes AI and AII).

B. Poor Myocardial Status.—The myocardial status of patients in this series deserves separate mention as a major if uncontrollable and poorly defined etiologic factor in digitalis intoxication. Indeed, poor myocardial status was almost constant in the group of patients considered here, for obvious reasons. It was felt to be an etiologic factor of great importance in 29 (73%) of the 40 patients studied because of the ease with which these patients became toxic on "average" or only slightly augmented dosage of digitalis preparations. For other statistical data and interpretation, see the section on severity of heart disease, above. Obviously little can be done to alter this factor. It is emphasized here rather to point out again that patients with poor myocardia are indeed more sensitive to intoxication by the drug which they need most for myocardial support. This classification of etiology corresponds to "patient's disease," a classification which is so popular at mortality conferences but which is all too often utilized to cover many sins.

C. Electrolyte Imbalance.—Lown and Levine [6] state that "small amounts of digitalis can initiate grave arrhythmias, even after the patient has been without digitalis for [some time], in the presence of electrolye derangements." In eight cases (20%) in this series it was felt that electrolyte abnormalities played a prominent role in the etiology of toxicity. In four of these, electrolyte changes were felt to be directly culpable. In the other four, overdosage was also implicated.

1. Potassium Deficit: Potassium deficit has been incriminated in digitalis intoxication associated with acute myocardial infarction, pulmonary embolism, acute infections, and other limiting conditions, as well as in cases of intoxication associated with diuresis. Lown, Salzberg, Enselberg, and Weston [17] suggest that a nonspecific stress response is involved with potassium loss in the urine and a redistribution of intracellular (and myocardial) potassium. No consistent lowering of serum potassium is reported. Total body potassium, however, is evidently decreased, and a redistribution must take place in the various intracellular compartments, including the myocardium. It has been possible to produce digitalis intoxication by hemodialysis with potassium withdrawal.[6,18] The dosage of digitalis sufficient to produce toxicity is appreciably reduced and the duration extended by a potassium depletion.[6] Digitalis toxicity may be abolished in man and animals by administration of potassium, even with normal serum levels.[6,7] Administration of carbohydrate by mouth or intravenously by Page [19] produced ventricular premature beats in six patients and ventricular tachycardia in

one patient, all of whom were at or near the point of toxicity to start with. Hypertonic saline can also do this.[21] Finally, Schwedel,[3] states that the excretion of potassium—normally 40 to 50 mEq. per day—may be doubled with a mercurial-induced diuresis. "Redigitalization" after diuresis is well described by Lown and Levine.[6]

Redistribution or loss of potassium then can evidently precipitate digitalis toxicity via a variety of mechanisms. Some of these are here illustrated.

(*a*) Diuresis. In all, 15 of the 40 patients underwent a diuresis within 48 hours prior to toxicity. There was no diuresis in 14 patients. In 11 patients this could not be evaluated. In only 4 of the 15 cases, moreover, could the diuresis be implicated as a major cause of intoxication. Three mechanisms were involved in these cases. One patient had uncontrolled diabetes mellitus and was admitted in diabetic acidosis, with a serum potassium value of 3.9 mEq. A second had a massive diuresis associated with control of congestive failure, which was quickly followed by digitalis intoxication. The other two patients showed symptoms and signs of toxicity after four- and three-day courses of mercurials in the hospital, respectively. Both had been receiving 0.15 mg. of digitoxin daily for long periods of time prior to admission without toxicity.

(*b*) Infusion of hypertonic saline to correct a low-salt syndrome.

A 72-year-old white woman was admitted to the Albert Einstein Medical Center, Northern Division, with the diagnosis of chronic inactive rheumatic heart disease, with mitral insufficiency, auricular fibrillation, and congestive heart failure, Class IVe. She had been given a maintenance dose of 0.25 mg. of digoxin daily for some time prior to admission and was maintained on 0.25 to 0.5 mg. daily during the week prior to toxicity. Because of very low serum sodium and chlorides she was given 100 cc. of 5% NaCl 48 hours prior to toxicity and again 24 hours prior to toxicity. She was also given 2 gm. of NaCl t. i. d. by mouth. On the day of toxicity she developed bigeminal rhythm while her heart was being examined. ECG revealed unifocal multiform ventricular extrasystoles in coupled rhythm. The bigeminy subsided after two days of oral KCl in orange juice. Infusion of KCl with the hypertonic saline might have prevented toxicity in this case.

(*c*) Vomiting and diarrhea. In one case toxicity was attributed to electrolyte imbalance induced by chronic diarrhea and vomiting. A dosage of 0.2 mg. of digitoxin was continued despite these symptoms, and the patient developed frequent ventricular premature superimposed on flutter with varying block and eventually died. The etiology of diarrhea and vomiting and the cause of death were both unexplained at postmortem examination.

II. Calcium Therapy: Bower and Mengle[20] reported two sudden deaths from the administration of calcium intravenously to fully digitalized patients. Two cases were reported also by Herrmann, Decherd, and McKinley.[1] Two additional cases are here tetany and a serum Ca value of 6.7 mg., 10 recorded. One patient died suddenly 10 minutes after receiving calcium gluconate intravenously. She was a 72-year-old white woman with congestive heart failure and uremia who was rapidly digitalized over a 24-hour period with 1.4 mg. of lanatoside C (Cedilanid). Because of the development of cc. of 10% Ca gluconate was administered intravenously. She died suddenly 10 minutes later.

The second case was that of a 63-year-old white woman with arteriosclerotic heart disease, hypertensive cardiovascular disease, and congestive heart failure, Class IVd. She was receiving 0.5 mg. of digoxin daily for 25 days prior to toxicity. On admission, studies revealed a potassium value of 4.1 mEq.; CO_2-combining power, 36, and calcium, 7.4 mg. This picture was attributed to a carcinoma of the colon, with chronic diarrhea. Because of the low calcium value she was given 10 cc. of 10% Ca gluconate daily intravenously, with the development on the third day of therapy of nausea, vomiting, anorexia, malaise, disorientation, and bigeminy due to frequent ventricular prematures. She also developed a nodal rhythm. The entire picture, including symptoms, bigeminy, and nodal rhythm, returned to normal after cessation of digoxin therapy and oral potassium chloride.

D. Limiting Conditions.—The most important of these conditions have already been discussed, namely, advanced congestive heart failure, with its accompanying poor myo-

cardial status, electrolyte imbalance, myocardial infarction, pulmonary embolism, and hypothyroidism. In addition, advanced renal disease was felt to play an important role in the etiology of toxicity in three cases reported here, presumably by way of failure to excrete the drug. (These patients were all oliguric.) Advanced liver disease has also been implicated, but no such cases are here recorded.

Gravity of the Syndrome of Digitalis Intoxication

Page [19] states that "the precipitation of fatal ventricular arrhythmias is the cardinal hazard of digitalis therapy. Frequently the appearance of ventricular extrasystoles heralds the onset of an ominous sequence which, in the presence of the underlying structural heart disease, progresses to ventricular tachycardia and ultimately to ventricular fibrillation." Lown and Levine [6] feel that once toxicity emerges a substantial percentage of the fatal dose has been administered. In the series of cases here reported, and using arbitrary criteria, 13 cases (33%) were regarded as "severe." These patients exhibited signs varying from frequent ventricular prematures to ventricular tachycardia and death in two cases. "Moderately severe" reactions were attributed to digitalis in 19 cases (48%). Only eight cases in this series (20%) would be classified by the conscientious internist as "mild." Many other deaths occurred, of course, during the period of toxicity, but these could usually not be attributed to digitalis because of the poor myocardial status of these patients.

Therapy

Potassium has been shown to be of value in two ways in varying arrhythmias due to digitalis intoxication. In the first place, it is said to have an intrinsic depressing effect on myocardial irritable foci.[8] Secondly, toxic doses of digitalis are capable of depleting heart muscle of potassium.[15] Since most patients in this series were treated with oral potassium chloride as well as by stopping digitalis, it was possible to gain some idea of the effects of this form of therapy. In five patients intoxicated by digoxin the average time for disappearance of symptoms or signs after oral potassium chloride (usually 1-2 gm. of potassium chloride five times a day) and discontinuation of the drug was 65 hours (two to three days). In nine patients receiving digitoxin the average time was 9 days in four patients who were receiving similar therapy and 11 days in five patients in whom toxicity was terminated by discontinuation of the drug without potassium therapy.

Summary and Conclusions

Forty selected cases of digitalis intoxication were studied, especially with regard to the etiology of toxicity in terms of correctable human error. Definite clinical criteria were applied to exclude doubtful cases. Age was not found to be a barrier to effective therapeutic exhibition of digitalis. The type of heart disease was not significant when compared to nontoxic controls. Acute myocardial infarction, however, seemed to predispose to development of toxicity in three cases.

The occurrence of signs of intoxication without symptoms was not a factor in the etiology of toxicity in this group, probably because of selection of severer cases. There was evidence, however, that digitoxin produced severer toxicity with fewer warning gastrointestinal symptoms than did digoxin. Nausea and vomiting were the most prominent symptoms by far, but anorexia may often be missed as an early symptom of intoxication. "Neurologic" symptoms are again emphasized as a common manifestation of digitalis intoxication, but these were usually accompanied also by gastrointestinal symptoms in this series of patients. Ninety-three per cent of cases in this series were found to have pulse irregularities; bradycardia was found in twenty-five per cent. The average P-R interval was 0.23 seconds in the intoxicated group, as compared with

0.19 seconds in nontoxic controls. The presence of "digitalis effects" by ECG was not a significant criterion of the presence of or severity of intoxication. Arrhythmias by ECG were present, however, in 95% of cases. Auricular fibrillation was attributable to digitalis intoxication in only 3 of 14 cases reported with this arrhythmia and was accompanied by other arrhythmias in 11 of these 14 cases. Bigeminy was present in 25% of cases of intoxication. Sixty per cent of patients with bigeminy also had auricular fibrillation. Only 20%, however, were associated with known rheumatic heart disease.

Six cases of refractory heart failure are reported, five of whom improved with the withdrawal of digitalis. Failure to attribute advancing congestive heart failure to digitalis intoxication may be a serious and not uncommon error. It is felt that when clinical signs and symptoms are compatible with both congestive heart failure and with digitalis intoxication, and if the congestive failure has not previously responded to adequate digitalis dosage, benefit will often be obtained by stopping or reducing dosage of digitalis rather than increasing dosage to the point of toxicity or by exhibiting potassium or procainamide.

A classification of etiology of digitalis intoxication is suggested which is based on correctable human error in the use of the drug. Eighty per cent of cases here reported were felt to have been preventable by attending physicians, and eighty-eight per cent of these could be attributed to errors in dosage. A common error, responsible for nine cases (23%) of toxicity here reported, was an attempt to control intractable failure by exhibiting high-maintenance dosage or by adding frequent small supplementary doses to an already adequate maintenance dose. It is suggested again that many of these patients may have evinced increased signs and symptoms of failure as a result of, as well as in spite of, augmented digitalis dosage. If dosage is to be increased in such cases it is suggested that frequent ECG's and careful observation, preferably in a hospital, be performed in order to spot early signs or symptoms of intoxication. Small increases of dosage are especially hazardous in patients with any of the well-known limitations to digitalis therapy, namely, poor myocardial status, electrolyte imbalance due to diuresis and congestive failure, acute myocardial infarction, pulmonary embolism, severe kidney disease (especially with oliguria), and advanced liver disease.

A commoner and insidious error was the failure of physicians to frequently follow up patients who were receiving relatively normal maintenance dosage of digitalis preparations. The follow-up was inadequate to individualize these so-called "normal" doses and especially to reevaluate patients' dosage on the basis of advancing congestive failure and other criteria already mentioned which may predispose to digitalis intoxication. The most frequent offending dosage in this series was 0.2 mg. of digitoxin daily and 0.5 mg. of digoxin daily; but toxicity developed in patients receiving 0.15 and even 0.1 mg. of digitoxin. Individualization and reevaluation of dosage are emphasized.

Electrolyte imbalance was prominent in eight cases in this series, but in only four of these (10%) could electrolyte imbalance be primarily indicted for the occurrence of toxicity. Two cases of toxicity associated with intravenous Ca therapy are reported. One resulted in sudden death. Diuresis was common but was felt to be primarily responsible for the development of toxicity in only four cases in this series (10%). Infusion of hypertonic saline probably precipitated intoxication in one case.

The potential gravity of the syndrome of digitalis intoxication is emphasized. Finally, the results of therapy with oral potassium and by discontinuation of digitalis are evaluated. In a small number of cases the average time for disappearance of symptoms or signs due to digoxin was 2 to 3 days; with digitoxin, 9 to 11 days.

Albert Einstein Medical Center, Northern Division, York & Tabor Rds. (41).

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Traumatic Involvement of the Thoracic Aorta

WILLIAM F. MAZZITELLO, M.D., St. Paul

Traumatic involvement of the thoracic aorta is of increasing incidence in this highly mechanical age. The early recognition of this condition is important in view of possible surgical intervention. However, considerable diagnostic difficulty may be encountered by the examiner because of the marked degree of variations in the clinical picture.

Three cases of involvement of the thoracic aorta following trauma to the thoracic cage are described in detail, and the vagaries of expression of such involvement are enumerated.

Report of Cases

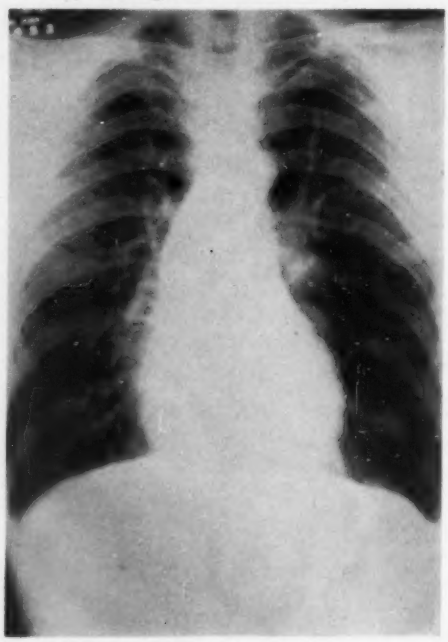
CASE 1.—A 47-year-old white man was admitted to Ancker Hospital on Nov. 30, 1953, with a chief complaint of severe persistent substernal pain which radiated up into the neck. The severe component of the pain began about one week previous to admission. History was elicited to the effect that he had been involved in an argument in the latter part of August of the same year, at which time he had experienced blows and kicks to the anterior chest. He had had a moderate degree of substernal pain and discomfort, which had gradually increased in intensity to the time of admission.

This pain was described as radiating to both shoulder blades, down both arms, and into the back and at times it was accompanied by occasional episodes of dull aching pain behind the eyes. The patient had occasional episodes of pain in the back, which progressed upward into the neck, during which time he would experience dizziness. When the pain reached the temple region the dizziness would regress and his vision would clear. Profuse sweating was noted. Past history failed to reveal any evidence of previous cardiovascular disease.

Blood pressure was 124/70. Pulse was 96 and regular. Pertinent physical findings were limited to the chest. The apex beat was located in the midclavicular line, fifth intercostal space, and the heart was not enlarged on percussion. There was a Grade 3 diastolic murmur heard over the entire precordium and loudest at the apical region. The aortic second sound was altered. A Grade 2 systolic murmur was heard over the aortic area. There were moist rales posteriorly at the bases of both lungs.

Serologic studies were negative. The venous pressure was 9.2 cm., and circulation time (dehydrocholic acid [Decholin]), 22 seconds. Cardiac fluoroscopy revealed suggestion of enlargement of left ventricle and exaggerated pulsations during

Fig. 1.—Posteroanterior film of chest, taken on admission, shows widening of the cardiac silhouette and of the ascending aorta. Increased prominence of the pulmonary vascular shadows are seen bilaterally, radiating out from the hilum.



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From the Departments of Internal Medicine, Ancker Hospital, St. Paul, and the University of Minnesota, Minneapolis; Assistant Professor of Medicine, University of Minnesota Medical School.

Fig. 2.—Posteroanterior film of the chest, two years previous to Figure 1. Note the normal cardiac silhouette and aortic shadow as contrasted to that in Figure 1.

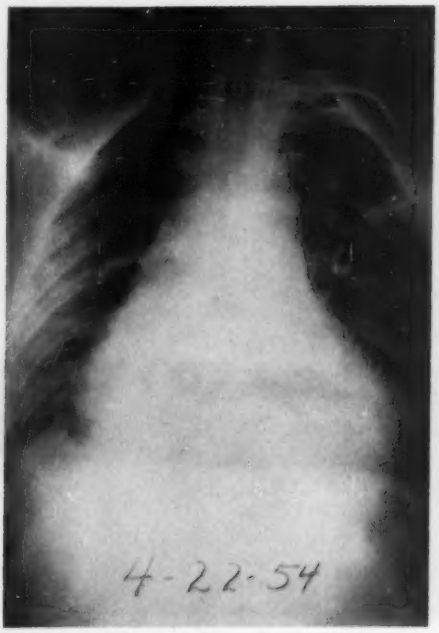


Fig. 3.—Posteroanterior film of chest, taken approximately two weeks before death, showing the marked degree of mediastinal and cardiac widening.

diastole. Posteroanterior film of chest revealed widening of the cardiac silhouette when compared to chest film taken two years previously (Figs. 1 and 2). Initially he was treated symptomatically until manifestations of congestive heart failure were noted. In addition to opiates and sedatives, when required, the patient was given digitoxin, a low-salt diet, and mercurial diuretics. He was discharged from the hospital and was followed in the outpatient cardiac clinic. Serial chest x-rays showed progressive cardiac enlargement. During this period of follow-up, three readmissions were necessary. Redigitalization, mercurial diuretics, low-salt diet, and bed rest were necessary to bring about cardiac compensation. At the time of his last admission (Fig. 3), April, 1954, severe cardiac decompensation was noted to be present. Progressive cardiac enlargement had taken place since time of initial admission. The circulation time was 37 seconds (dehydrocholic acid), and the venous pressure was 29.3 cm. of citrate. The clinical course was progressively downhill, and he died May 5, 1954.

During the period of this last admission, urine examination had revealed 1+ albumin, hyaline casts, and occasional white and red blood cells. The BUN during this terminal phase was 43 mg. per 100 cc. Serial electrocardiograms had failed to reveal any significant findings except a pattern of left ventricular hypertrophy. The intensity of the diastolic murmur during this last admission had increased to Grade 4, and peripheral vascular signs compatible with aortic insufficiency were present.

Gross Autopsy Findings.—Thorax: Both pleural cavities are found to be free of adhesions, and to contain about 300 cc. of bloody fluid each. The pericardial sac contains approximately 75 cc. of clear straw-colored fluid. The heart measures 16 cm. in transverse diameter. Examination of the pulmonary artery reveals an embolus in one of the main branches on the right.

Heart: The heart weighs 465 gm. The valves are normal throughout. The coronary arteries show a moderate degree of atheromatous streaking and plaque formation throughout, but their lumina are widely patent. The right ventricle is moderately dilated, and the left ventricle is markedly dilated, with normal appearance of the myocardium on section. The root of the aorta shows a few atheromatous plaques. Just above the posterior cusp of the aortic valve there is a T-shaped tear in the intima, measuring 2.5 cm. (Fig. 4). At a point just proximal to the origin of the

Fig. 4.—The heart is opened to present complete exposure of the left ventricle and aortic valve. Immediately above the posterior cusp are parallel tears through the intima, with several other small intimal tears superiorly. Wrinkling of the aorta is noted, with separation of the wall. Hypertrophy of the left ventricle is prominent.

innominate artery there is a transverse tear in the aorta, measuring 4 cm. in length. Between the above-described tears the ascending aorta shows a false passage in its wall, which measures 4 to 5 cm. in width. The lining of this false passage is smooth and is free of adherent blood clot. The false passage extends into the sinus of Valsalva of the posterior aortic cusp. The sinuses of Valsalva of the right and left aortic cusps and the coronary artery orifices are not involved. The atria and auricular appendages are free of thrombi.

Lungs: The right lung weighs 890 gm. The surfaces are smooth. There is consolidation of the posterior segment of the right upper lobe, the lateral segment of the right middle lobe, and the apical segment of the right lower lobe. On section these areas as well as smaller areas throughout the right lower lobe are seen to be deeply hemorrhagic. Elsewhere the lung substance shows marked congestion, and an excess of fluid is present. The smaller radicles of the pulmonary artery adjacent to and in the above-described areas of consolidation contain adherent antemortem blood clots. The left lung weighs 412 gm. The surfaces are free. On section there is a slight excess of fluid, and some congestion is present.

Aorta: Examination of the descending portion of the thoracic aorta shows it to be free from atheromatous streaking.

Microscopic Findings.—Aorta: Sections show the false passage described above to have an endothelial lining (Fig. 5). The wall of the aorta appears to be normal. In the adventitia and in the fat external to the aorta there is an area where there is a large collection of lymphocytes. In this area there are several spaces which appear to be blood spaces which have a prominent endothelial lining.

Fig. 5.—Section through the wall of the aorta shows normal wall to the left and double wall to the right, with false passage clearly outlined.

Lungs: Sections show marked congestion throughout. Sections of the consolidated areas in the right lung show scattered areas of infarction which are hemorrhagic in appearance.

CASE 2.—A 23-year-old white man who entered the hospital Feb. 1, 1955, with chief complaints of weakness, coldness of the legs, and abdominal pain of a constant severe nature. The onset of this pain had been noted the previous morning, at which time a severe dizzy spell had been experienced. Involuntary stools and urinary incontinence as well as nausea and vomiting had occurred the day of admission. Past history revealed that the patient had been in an automobile accident in November, 1954, at which time a 24-hour period of unconsciousness had been experienced while he was being taken care of at home. X-ray examinations had not been done, nor had the patient been hospitalized. After a short period of convalescence at home he had returned to work. However, frequent dizzy spells were noted, at times of such a severe nature as to prevent him from working.

Physical examination revealed a white man who appeared pale and restless. Pulse was 130 per minute and regular. Blood pressure was 170/90. Numerous moist inspiratory rales were noted throughout both lung fields. The heart tones were of good quality, and no murmurs were described. The peripheral pulses were unobtainable in the right arm and both legs, and the involved extremities were cool. Neurological examination was negative.

Posteroanterior films of the chest (Fig. 6) revealed widening of the mediastinum to the right. In the right midhilar region there was noted a shadow suggestive of a dissecting aneurysm. A spinal tap was done, with opening pressure of 240 mm. of H_2O and dosing pressure of 210 mm. of H_2O being recorded. Spinal fluid analysis was negative. Hemoglobin was 17 gm. per 100 cc.; white blood cells, 25,850, with 78% polymorphonuclear leukocytes, 14% lymphocytes, 5% monocytes, 3% myelocytes, and 1% normoblasts.

An ECG was done shortly after admission and revealed an anterior myocardial infarction of undeterminate age. Six hours after admission the patient suddenly died. A complete postmortem examination was done, and the pertinent findings are as follows.

Gross Autopsy Findings.—Thorax: The right lung is adherent over the apical portion. The right pleural cavity contains about 400 cc. and the left, approximately 300 cc. of straw-colored fluid. The pericardial sac contains approximately 500 cc. of blood-tinged fluid. The heart measures 15 cm. in transverse diameter. Examination of the large branches of the pulmonary artery shows no evidence of thrombi or emboli.

Fig. 6.—Posteroanterior film of chest, showing mediastinal widening, with prominence along the right hilar region. Accentuation of the hilar vascular shadows bilaterally is also evident.

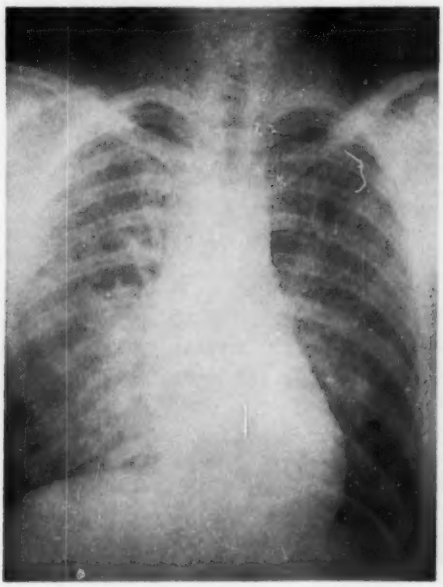


Fig. 7.—The arrow points to a partially circumferential transverse tear through the proximal aorta, resulting in dissection superiorly and inferiorly. The cut at right angles to the transverse tear was made at autopsy.

Fig. 8.—Microscopic section shows dissection occurring in the media of the aorta, with numerous red cells visualized in the lower portion of the dissected wall.

Heart: The heart weighs 440 gm. The valves are normal in appearance. The coronary arteries show no evidence of sclerosis. The myocardium on section shows no gross evidence of fibrosis or infarction. The root of the aorta is definitely dilated and thin-walled. At a point 2.5 cm. distal to the aortic ring (Fig. 7) there is a ragged tear in the intima and a portion of the media. This rent measures 8 cm. in length and is almost circumferential. The outer media and adventitia form a second tube, and the dissection has extended downward to the root of the aorta, where the hemorrhage definitely surrounds the right coronary artery near the orifice. The dissection extends upward into the innominate artery an undetermined distance. Just distal to the left subclavian artery the intima of the aorta shows a slight ridge, and its lumen appears to be slightly narrowed at this point. There is some hemorrhage in the adventitia of the aorta downward to a point about halfway through the thoracic aorta. The auricular appendages show no thrombi.

Microscopic Findings.—Aorta (Fig. 8): Sections through the aorta in the region of the dissection show the media to be split at a point about midway between the intima and the adventitia. The sections show the angle at which the actual splitting terminated at this point into the dissection. The inner portion of the media shows scattered areas of mucoid degeneration, and in the angle small areas of thrombosis are seen. There is no evidence of an exudative inflammatory

Fig. 9.—Section of myocardium shows polymorphonuclear-cell infiltration and tinctorial changes of acute myocardial degeneration. This latter is most prominent in the lower right-hand corner.

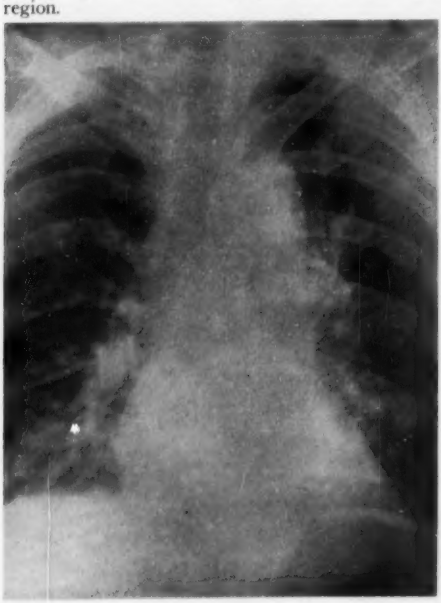
process in the media, but a few perivascular collections of lymphocytes are seen in the adventitia.

Myocardium (Fig. 9): Sections through the myocardium show edema, which separates the cardiac-muscle bundles. In many areas throughout these edematous areas there is a diffuse acute inflammatory infiltration. There is no evidence of infarction of the myocardium, however. At the margins of the edematous areas some of the muscle cells show a decrease in striations and a slight difference in staining reaction. This process may be attributable to the occlusion of the right coronary artery by the dissecting aneurysm.

CASE 3.—A 41-year-old white man was admitted to the hospital on July 24, 1955, following a fall from a second-story staircase while assisting two other men in carrying a refrigerator. Acute onset of pain in the chest and left hip were complained of, and an alcoholic odor was noted on his breath. Within 15 minutes after admission the blood pressure fell from 110/50 to 95/50. Administration of 1000 cc. of 6% dextran was started intravenously, and the blood pressure temporarily stabilized at 124/68.

Physical examination revealed crepitus over the right clavicle, with clear breath sounds heard throughout both lungs. Heart tones were of good quality, and a regular rhythm was present. No murmurs were heard. Abdominal examination was negative. There was inability to flex the left hip or to extend the left knee.

Fig. 10.—Posteroanterior film of chest shows mediastinal widening, most clearly evident in the superior mediastinum, with accentuation of the pulmonary vessels most prominent in the hilar region.



X-rays (Fig. 10) revealed fractures of the right clavicle and several ribs on the right. Prominent mediastinal widening was noted, with increase in the hilar vascular shadows. No pleural fluid was noted. The hemoglobin varied between 8.8 and 6.9 gm. per 100 cc. in spite of the transfusion of several pints of whole blood, and the blood pressure persisted near hypotensive levels during the remainder of the evening. At 2 a. m. of the following morning tachypnea was noted, and chest examination revealed moist crackling rales on inspiration and considerable decrease in breath sounds over the left anterior chest. The heart sounds were reduced in intensity, but a regular rapid rate was present. No murmurs were noted. Hepatomegaly, splenomegaly, and positive abdominal findings were absent. The blood pressure continued to drop in spite of continued transfusion, and the patient died one hour later. Cardiac massage was attempted.

Gross Autopsy Findings.—Thorax: The fourth, fifth, and sixth ribs on the left have been cut at the costochondral junction. The muscles and other structures in the fifth interspace have been separated beneath the surgical incision mentioned above. The right lung shows fibrous adhesions at the apex and several emphysematous blebs in this region. The right pleural cavity contains approximately 1500 cc. of fluid and clotted blood. There is a fracture of the right clavicle and of Ribs 2, 3, 4, 5, 6, 7, 8, 9, and 11 on the right side. The fractures run in a curvilinear oblique fashion from forward to the posterior on the way downward. The left lung is free from adhesions, and the left pleural cavity contains approximately 1500 cc. of fluid and clotted blood. The mediastinum on the left side is seen to be full of blood, and there is a tear in the pleura just in the midlateral portion of the mediastinum. There are no rib fractures on the left side. The pericardial sac shows no adhesions and contains no excess fluid. The heart measures 14.5 cm. in transverse diameter. Examination of the large branches of the pulmonary artery shows no evidence of thrombi or emboli.

Heart: The heart weighs approximately 410 gm. The valves appear normal. The coronary arteries show no evidence of atheromatous plaque formation, thrombus, or embolus. The myocardium on cut section shows normal structure. The root of the aorta shows moderate atheromatous streaking and plaque formation. On the inner circumference of the arch of the aorta about 1.5 cm. distal from the origin of the left subclavian artery (Fig. 11) there is a transverse tear measuring about 2 cm. in length. This lies in the superior portion of an atheromatous plaque. Another atheromatous plaque is seen just above this. The auricular appendages and atria show nothing of note.

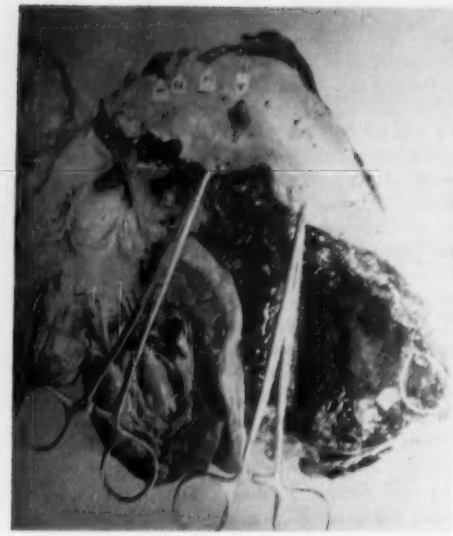


Fig. 11.—The aorta is laid open, with Arrow 1 indicating origin of the innominate artery; Arrow 2, indicating the left common carotid, and Arrow 3, the left subclavian artery. Arrow 4 points to the laceration in the isthmus region of the aorta, and evidence of mediastinal hemorrhage may be seen immediately below the proximal edge of the aorta in this same region.

Microscopic Findings.—Heart: Sections through the myocardium show normal findings.

Lungs: Sections through the lungs show collapse of the alveoli. Some of them still contain a few red blood cells and some brown pigment-laden macrophages. There is no evidence of pneumonia.

Aorta: (Fig. 12) Sections of the aorta in the region of the tear described grossly show no actual splitting of the media, but the rent extends through all layers of the media, and blood and acute and chronic inflammatory cells diffusely infiltrate the adventitia of the vessel. At the point of rupture various areas of thrombosis are seen.

Review of the Literature

One of the most important articles dealing with traumatic pathology of the aorta was written by Strassman,[1] in 1947. In this study he reviewed 7000 autopsies from the Medical Examiner's Office, New York, during the years 1936-1942 and found 72 cases of traumatic rupture. Of these 72, there were 57 men and 15 women. The ages varied from two cases under 10 years to two cases over 80. Forty-two cases were less than 50 years old, and thirty cases were over 50.

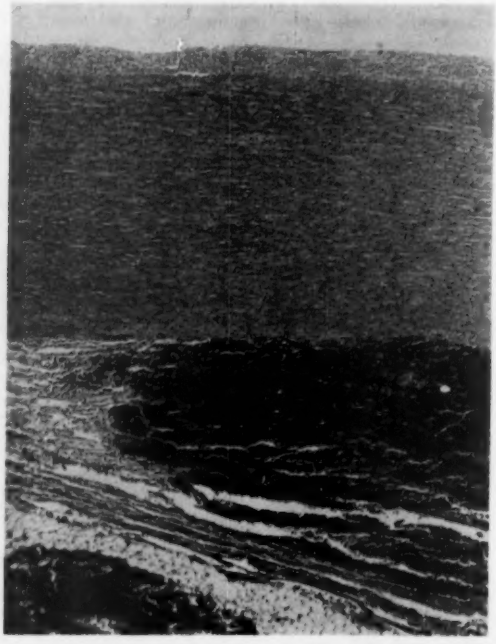


Fig. 12.—Microscopic section, showing the hemorrhagic dissection occurring through the wall of the aorta. In this depicted area the media and adventitia are principally involved.

The principal etiologic factor was automobile accidents, 51 cases in all. This included pedestrians as well as the drivers. In 61 cases the aorta had ruptured in only one site, while in 11 cases the vessel was torn in two or more sites. The most important site of traumatic rupture was at the region of the aorta immediately below the insertion of Botal's ligament. Forty cases were recorded by Strassman to have occurred at this site. In 15 cases rupture had occurred between the isthmus and the diaphragmatic opening, and in 3 cases the abdominal aorta had been involved. Rupture of the ascending aorta immediately above the aortic valves had taken place in 14 cases.

Strassman's [1] observation concerning the macroscopic site of involvement was also of particular interest. He mentions that in almost all cases rupture occurred in a transverse direction through the wall of the vessel. Only a few T-shaped or longitudinal tears were encountered. The rupture was complete and had perforated all layers of the wall, including the adventitia, in 64 cases. In eight cases the adventitia was still preserved and was dissected from the media by the hemorrhage resulting from the rupture. It is interesting to note that in only one case was slight hemorrhage observed in the pericardial sac.

The time of death following the accident varied as follows. Fifty-nine patients died within one hour, and in these instances the rupture was complete and extended through all layers of the wall. Six patients lived 1 to 3 hours; three, from 5 to 7 hours, and four, from 12 to 18 hours after the accident. Eight cases lived for at least three hours, and in these cases the rupture was incomplete with intact adventitia.

Other reports in the literature tend to substantiate the basic concepts of Strassman.[1]

Leonard,[2] in 1945, reported the case of a 60-year-old man pinned against the steering wheel after an automobile accident. Shortly after extrication the patient suddenly died, and autopsy revealed a transverse fracture through the manubrium, left hemothorax, a rent in the mediastinal pleura, and a dissecting aneurysm of the first part of the descending aorta at a point adjacent to the body of the fourth dorsal vertebra. The media had been dissected away from the adventitia, with subsequent rupture of the latter and hemorrhage into the left pleural cavity.

The case of a 20-year-old white woman was reported by Rice and Wittstruck,[3] in 1951. This patient, while riding in a taxicab, had been suddenly thrown against the back of the front seat when an accident took place. An immediate onset of chest pain with gradual development of hypertension was noted. Death occurred suddenly 20 days later. Postmortem examination revealed a transverse laceration through the inner coats of the thoracic aorta at a point just distal to the left subclavian branch and the attachment of the ligamentum arteriosum. The laceration involved the whole circumference of the aorta except for a small anterior portion. It extended through the intima and had dissected as well to the celiac artery. The mediastinum was filled with blood.

A somewhat longer post-traumatic survival time is seen to occur in the four cases reported by Hollingsworth, Johnston, and McCooey.[4] All their cases were males with ages ranging from 19-33. Two cases of saccular aneurysm of the descending thoracic aorta were noted. In another case angiograms revealed an aneurysm arising from the left aspect of the transverse portion of the aortic arch. In the last case mediastinal widening had been noted, but two weeks later a repeat film of the chest had revealed complete disappearance of the mediastinal shadow. A follow-up of seven years in this last case revealed no subsequent changes.

Kastl,[5] in 1953, reported the case of a 33-year-old white man involved in an automobile accident. Substernal pain had been complained of on admission, and serosanguinous fluid had been found in the left pleural cavity. The patient died 10 days later, and postmortem study showed presence of fresh

clotted blood in the left pleural cavity, which was found to have originated from a 1 cm. rent in the mediastinal pleura at the hilum of the lung. This was opened widely, and an organized clot was found. Removal of this clot revealed a complete transection of the aorta just distal to the left subclavian artery.

Four cases of traumatic rupture were reported in 1953 by Wyman.[6] Two were men 51 and 91, respectively, and both had been struck by an automobile. A complete transverse rupture of the aortic arch just above the pericardial reflexion, with massive mediastinal hemorrhage, was found in the first case. In the other case, a 91-year-old man, a sharply delineated laceration was noted 5 cm. below the origin of the left subclavian artery. This was almost circumferential in its involvement. The third case report was that of a 49-year-old woman who had been involved in an automobile accident. Mediastinal widening had been noted on x-ray shortly after the accident. Eight days later a left hemothorax was noted, and patient died shortly thereafter. A transverse laceration 4 cm. in length was found in the descending aorta. This rent was associated with an atherosclerotic plaque. The last case was also a woman, 49 years old, who experienced severe chest pain and dyspnea after an automobile accident. X-rays had revealed mediastinal widening. Gradual recovery ensued, however, with disappearance of the highly suggestive x-ray changes of mediastinal widening.

The predilection for the involvement of the isthmus portion of the aorta is explained by Strassman,[1] in that the aorta is narrowed at this site and fixed by the ligamentum arteriosum. Another theory which attempts to explain the frequency of involvement of the isthmus portion of the thoracic aorta is that of Haas.[7] "Whenever one part of the body decelerates at a rate different from that of another part, the connection between these two parts is placed under stress proportional to the rates of deceleration. Thus during horizontal deceleration of the thorax, the mobile aorta is slowed at a different rate than the arch which is relatively fixed. The aorta with its column of blood is thrown forward exerting a maximum pull at the isthmus, the junction of these two different decelerating structures."

Rice and Wittstruck[8] state that "in linear deceleration of the thorax, the central portion of the descending aorta, being the least rigidly bound, is snapped forward by the momentum of the deceleration force and the mass of the aorta's content of blood." Basically this concept refers to the point of fixation of the arch of the aorta by the great vessels and the ligamentum arteriosum as inferred by Strassman.[1] The fundamental concept is similar to that of Haas.[7]

The involvement of the proximal portion of the ascending aorta by trauma resulting in tearing and dissection may also be explained by the relative fixation of the heart and the arch. The aorta between these two points is relatively mobile and thus is also susceptible to sudden changes in linear deceleration. Warfield[8] felt that the aorta in its root portion may be relatively less fixed than the heart, which is immobilized by the expanded lungs during full inspiration. This theory has some support from the observation of Peery,[9] who feels that the valve commissures exert a rocking force on the sinuses of Valsalva, as they are forcibly closed during diastolic filling. This focal stress on the aortic root would tend to explain the frequency of transverse tears occurring in this region.

Comment

From the above review of the literature and the present case reports traumatic involvement of the thoracic aorta is seen to present a variable and deceptive clinical picture to the examiner. In instances where the isthmus portion of the aorta is involved a complete tear of various degree is invariably found to occur, usually producing hemorrhage into the mediastinum, the left pleural cavity, and occasionally both pleural cavities. Death occurs at varying periods of

hours after the onset. The clinical picture is usually catastrophic, as in our Case 3, featured by chest pain and significant fluctuations in pulse rate, blood pressure, state of consciousness, and hemoglobin level. Physical findings on chest examination may reveal rhonchi, inspiratory rales, and alterations of breath sounds over the left chest, with associated signs of pleural effusion. The chest x-ray may at times be the earliest to point out possible existence of such an occurrence by mediastinal widening and pleural effusion. The cases in the literature presenting pathologic and clinical features similar to our Case 3 are interesting in that they reveal the variable length of time, which, although short, may ensue before death occurs. In Leonard's [2] case death occurred almost within a few hours of the accident and certainly compares with duration of survival of our Case 3. This is in contrast to the case of Rice and Wittstruck,[3] who survived for 20 days. Other survivals were 10 days (Kastl [5]) and 8 days (Wyman [6]), with other survival times not being specifically mentioned. In Strassman's [1] series the majority of deaths occurred within the first hour.

In contrast to the above, not all cases showing involvement of the isthmus region of the aorta present a similar acute picture. There are instances in which an incomplete tear occurs, with subsequent gradual weakening and formation of a saccular aneurysm. Such are the cases reported by Hollingsworth et al.,[4] and in one of these a follow-up of seven years has been reported. It may be noted that none of the prominent clinical findings which were a feature of the cases with a complete tear were noted here. Only vague chest complaints were elicited, with no significant physical or laboratory findings. After a period of time had elapsed, however, repeat chest films brought out the prominent x-ray changes in the mediastinum, which were then correlated with a history of chest trauma in the past. This type of case appears to offer the best prognosis, since surgical excision of the saccular aneurysm has given good results to date.[4]

When the proximal portion of the thoracic aorta is involved, even greater vagaries in the clinical picture may ensue. This apparently is related to the specific location of the pathology. In our Case 1 the multiple intimal tears were located in the proximal part of the aorta near the annulus, with extension into the sinus of the posterior aortic leaflet, resulting in loss of support of the valve cusp. This gave rise to the gradual onset of diastolic and systolic murmurs over the precordium, and as time progressed these murmurs became very prominent and a clinical picture of aortic insufficiency resulted. Dissection of the aorta occurred superiorly. In our Case 2 the degree of involvement of the ascending aorta was more prominent, featured by a circumferential tear through the intima and partly through the media, with secondary dissection superiorly to involve the aortic arch branches and inferiorly to the root of the aorta, where compression of the proximal portion of the right coronary artery resulted in myocardial ischemia (Fig. 9). Some oozing into the pericardial sac was also noted, although cardiac tamponade per se was not present. In this case no murmurs were noted, although the patient had survived approximately three months. It is interesting to speculate that the relatively greater distance of the intimal tear from the annulus of aortic valve in this case did not cause any loss of structural support of the leaflets during diastolic, as occurred in our Case 1, and as a consequence murmurs were absent or not significantly audible at this time. The possibility of murmurs occurring at a later date cannot be overlooked, however. This observation is especially pertinent in regard to Peery's [9] quote of a case reported by Heller [10] of a 37-year-old man who had a traumatic episode with direct involvement of the anterior chest. Although chest pain and dyspnea were noted, it was not until one month later that a murmur was first heard, being systolic in character.

It is recognized that confusion may exist regarding the differential diagnosis of eti-

ology of the dissecting process when the proximal thoracic aorta is involved. In this regard hypertensive cardiovascular disease, Marfan's syndrome, syphilitic aortitis, and severe atherosclerotic degeneration would be more prominently considered.[11] In Case 1 the differential diagnosis on admission included a ruptured aortic cusp[9] as well as a dissecting aneurysm. A few scattered atheromatous plaques were noted in the proximal aorta in the region of the intimal tears but were not intimately associated with them. In Case 2 mucoid degeneration was noted in the section of the aorta in the vicinity of the circumferential tear. The admission blood pressure of 170/90 was considered incidental to the pathologic process,[3] as was the mucoid degeneration, since there was no history of hypertension nor were any of the classical features of Marfan's syndrome present. The electrocardiogram showed a pattern of an anterior myocardial infarction. However, the gross and microscopic studies of the myocardium did not reveal any areas of infarction, although the microscopic section did show an acute inflammatory reaction, with tinctorial changes suggestive of early degeneration. As was previously noted the coronary arteries on serial sectioning were normal in appearance.

In both cases of involvement of the proximal aorta vague symptoms of chest discomfort, dyspnea, and sense of precordial oppression were noted. These are not specific for pathology of the aorta, but when considered in view of the history of chest trauma a high index of suspicion follows. When the x-rays show characteristic widening of the mediastinum, as occurred in both of these cases, with gradual increase during follow-up studies, the complete evaluation of the above will then lend itself to a definite diagnosis.

In Case 3 the presence of several atherosclerotic plaques was noted in the region of the intimal tear, but it is quite unlikely that such minimal involvement would have caused a spontaneous tearing to occur. It is, however, difficult to deny the possibility of such atherosclerotic lesions predisposing to an increased degree of structural weakness at this region.

In general, therefore, evaluation of lesions of the isthmus portion of the thoracic aorta will not usually cause serious problems in the differential diagnosis. On the other hand, when the proximal aorta is involved a more complex differential diagnosis will be encountered. The major factors therefore in adequate evaluation of these patients would be a thorough history, especially in eliciting occurrence of recent chest trauma. A thorough physical examination should be done to detect presence of cardiac enlargement, cardiac murmurs of recent origin, and unilateral or bilateral changes in the lungs and pleural cavities, as well as evaluation of the vital signs. Of great importance also are the initial and follow-up chest films. If the above diagnostic routine is rigidly adhered to it is doubtful whether many of these cases would be overlooked or diagnosed in the late stages. The length of survival of our three cases was long enough for the institution of reparative surgical procedures. In our Case 3 the duration of survival after the fall was quite short, in agreement with the observations of others in lesions of this type.[1,2,5-7] However, immediate recognition and treatment of these cases may have been life-saving. It is recognized that these cases provide a formidable challenge to the thoracic surgeon, but with improving technique and skill many more of the patients may be saved. This is evidenced by the reports of Hardin,[13] Hollingsworth et al.,[4] and Creech et al.[14] It is important, therefore, for the examiner to hold a high index of suspicion regarding possible aortic pathology in cases of trauma to the chest wall. Complete diagnostic work-up at the time of the initial examination should be followed by periodic checks. If this is done earlier diagnoses will be made before irreversible changes have taken place, and timely corrective surgical procedures may be instituted.

Summary

Three cases of trauma to the chest wall with secondary involvement of the thoracic aorta are presented. Two cases had incomplete tears through and dissection of the proximal or ascending portion. A complete tear in the isthmus region with mediastinal hemorrhage was noted in the other. All three patients died.

The clinical and laboratory characteristics of these three cases are presented and discussed.

A review of the literature is presented, with summation of the predominant sites of pathology of the thoracic aorta after trauma.

The importance of early recognition of the underlying pathology is stressed in regard to the early institution of life-saving surgical measures.

Ancker Hospital (1).

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Diabetic Neuropathy: Pitfalls in Diagnosis

MAX ELLENBERG, M.D., New York

The entity of diabetic neuropathy has been recognized for many years. With increasing experience and recognition of this complication of diabetes, a broader appreciation of its clinical manifestations has taken place. Unfortunately, however, a basic confusion in diagnosis still exists. This results from the fact that the neurological syndromes are so numerous that almost any condition may be simulated. Nervous system involvement is frequently diffuse and disseminated and may present a bizarre picture. Further, the etiology, pathology, and treatment remain essentially unknown. The symptoms may indicate involvement of the peripheral nerves, the spinal roots, the spinal cord, the cerebrum, or any combination thereof.

The most frequent clinical picture is characterized by involvement of the nerves of the lower extremities, most often bilaterally symmetrical and predominantly sensory.[1] However, unilateral involvement may be present[2]; there may or may not be pain[3]; there may be severe pain, with a minimum of objective findings[4]; there may be absence of pain, with a multiplicity of findings[5]; there may be complete peripheral sensory loss without paralysis, or there may be grave paralysis with insignificant sensory involvement[6-8]; there may or may not be associated vascular changes; the diabetes may be mild or severe.[9] There may be cerebral involvement, as indicated by ocular-nerve palsies,[10-12] pupillary abnormalities[13]; trigeminal-[9,12] and facial-nerve involvement,[4] and occasionally emotional disturbances severe enough to lead to psychiatric diagnoses.[1,5,14] There may be autonomic-nerve and visceral involvement,[1,4,15] including changes in vasomotor,[9-16] pilomotor,[9] and sudomotor control[16,17]; dependent edema[1,9]; abnormality of texture and consistency of the skin[18]; neuropathic ulcers[1,9]; Charcot arthropathy[19,21]; impotence[22]; orthostatic hypotension[15,17,23]; neurogenic vesical dysfunction,[22,24,25] and neurogenic bowel dysfunction.[15,26-28] There may be a syndrome referred to as "pseudotabes diabetica," characterized by diminution or loss of deep reflexes, sensory changes, lightning pains, ataxia of the sensory type, bladder and bowel involvement, and pupillary abnormalities.[4,5]

Although it is frequently stated that neurologic involvement is associated with poor diabetic control,[1,9] paradoxically it may be precipitated coincident with the establishment of good control.[5,12] It may follow an episode of ketosis[1] or surgery[4] or suddenly appear after trauma.[4] On the other hand, it occasionally may be the initial clinical symptom of unsuspected or "latent" diabetes.[7,32,33]

In view of the complexity of the possible neurological picture there is little wonder that the clinical diagnosis is fraught with difficulty and error. To confuse the picture further, however, is the fact that there are no pathognomonic signs, symptoms, or laboratory findings to unquestionably establish or eliminate the diagnosis. Although elevation of the spinal fluid total protein has been frequently reported, it is not a constant finding, nor has any particular characteristic of the protein elevation been defined in this entity.[1,9,29-31] It is obvious, therefore, that the diagnosis must first be based on the exclusion of any and all other possible diagnoses plus the presence of certain suggestive signs and symptoms in the presence of

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From the Department of Medicine, The Mount Sinai Hospital; Assistant Attending Physician.

diabetes and strengthened by an elevation of spinal fluid protein.

In the past the diagnosis of diabetic neuropathy has frequently been overlooked and mistakenly diagnosed as syphilis, variants of sub-acute combined sclerosis, thiamine (vitamin B_1) deficiency, spinal cord tumors, cauda equina tumors, retroperitoneal neoplasms, gastrointestinal neoplasms, and prostatic obstructive uropathies.[3] More recently the pendulum has begun to swing in the other direction, and we have, in a fairly short period of time, collected several cases where the diagnosis of diabetic neuropathy was incorrectly made and the underlying pathology recognized only after a more or less prolonged period of observation and a more careful evaluation of the clinical picture. It is the purpose of this presentation to indicate that suggestive neurological signs and symptoms are in themselves insufficient to establish a diagnosis of diabetic neuropathy. This diagnostic error may well deprive the patient of proper therapy. The following case reports are presented.

Report of Cases

CASE 1.—This 41-year-old white woman was admitted to the medical service of the Mount Sinai Hospital because of a six months' history of diarrhea accompanied by a 20 lb. weight loss. There were no fever or other constitutional manifestations. The bowel movements numbered 3 to 10 per day but contained no blood, pus, or mucus. There were no other gastrointestinal manifestations. She denied any emotional upset. No sphincter disturbances were noted. For the past four months ankle edema had been present. The past history is significant in that she was a known diabetic for 30 years, with the age of onset at 11. She was well controlled on diet and 20 units of protamin zinc insulin injection each morning, although very sensitive to even minor fluctuations of this dosage. There had been transitory episodes of diarrhea at ages 18, 24, and 34.

On examination she appeared chronically ill, with heart and lungs normal; blood pressure 100/60; liver palpable at the costal margin. There was no abdominal tenderness; there was a 2+ ankle edema; neurological examination was negative; the fundi revealed no evidence of diabetic retinopathy. Laboratory examination showed the sedimentation rate to be 20 mm. in one hour; blood serology was negative; the urine contained 2+ albumin, with occasional white blood cells; hemoglobin, 11 gm., with normal red and white blood cell counts; platelets, 236,000 per cubic millimeter; hematocrit, 38%; blood CO_2, 43 vol.%; sodium, 136 mg. per 100 cc.; potassium, 3.9 mg. chlorides, 110 mg. per 100 cc.; cholesterol, 72 mg. per 100 cc.; alkaline phosphatase, 5.4 King-Armstrong units; total protein, 6.0 gm. per 100 cc., with globulin increased to 3.2 gm.; stool guaiac test yielded a 4+ reaction.

Because of the prolonged duration of the diarrhea without constitutional symptoms, the patient was admitted and initially treated for diabetic diarrhea. Further study, however, revealed findings compatible with and diagnostic of non-tropical sprue with malabsorption syndrome. The prothrombin time was 26.5 seconds, with control, 12.5; calcium 6.4, mg. per 100 cc.; phosphorus, 3.2 mg. per 100 cc.; vitamin A tolerance test showed a marked depression, the values being fasting, 7μg. per 100 cc.; four hours, 40μg.; six hours, 10μg., and eight hours, 6μg. Barium enema was negative; gastrointestinal series showed that the head of the barium meal was in the descending colon in three hours; the small intestine showed changes consisting of delayed segmentation, retained secretions, coarsening of the folds, and areas of marked dilatation consistent with sprue (Fig. 1). Further stool examination revealed large quantities of fat, with few fatty acid crystals. Findings on gastric analysis, pancreatic secretion studies, and sigmoidoscopy were normal. Therapy

Fig. 1.—X-ray of small intestine, Case 1. *Note* retained secretions, coarsening of the folds, delayed segmentation, and areas of marked dilatation.

was begun with liver extract and massive vitamin administration parenterally, with no improvement in the patient's condition. Following the use of hydrocortisone there was a dramatic response, with prompt and complete alleviation of symptoms and findings accompanied by a rapid weight gain of 10 lb. With the use of corticosteroids the insulin requirement increased to 60 units lente insulin daily, but the previous sensitivity to insulin disappeared.

Comment.—The presence of diarrhea without tenesmus, urgency, pus, blood, or mucus in a patient with diabetes of 30 years' duration had immediately suggested the diagnosis of diabetic diarrhea secondary to autonomic nerve involvement of the alimentary canal. Against this diagnosis is the fact that in the diarrhea associated with diabetes there are almost always associated neurologic findings consisting of peripheral neuropathy and/or pseudotabes diabetica. Further, the diarrhea is frequently nocturnal and very often associated with fecal incontinence. Fortunately, in this case the absence of confirmatory signs led to further investigation and the diagnosis of nontropical sprue. Specific therapy resulted in dramatic and prompt response.

CASE 2.—This 78-year-old white woman had known diabetes for 15 years, which had been well controlled with the intermittent use of insulin. Past history included coronary sclerosis, with a previous myocardial infarction and frequent episodes of angina pectoris, a cerebral vascular accident, and congestive heart failure requiring the occasional administration of meralluride (Mercuhydrin). The present illness began with complaints of discomfort in the low back region, with radiation down the posterior aspect of both lower extremities. The pain was increased by locomotion but was also intensified by lying in bed. She occasionally complained of some coldness in both lower extremities.

On examination, blood pressure was 130/80; pulse, 88 per minute; respirations, 18 per minute; pupils reacted to light and accommodation; there was a corneal arcus; fundi showed tortuousity of vessels, with no hemorrhages or exudates; the mouth was edentulous; thyroid, normal; neck veins, slightly distended; lungs, clear; heart, enlarged, with the apex beat 2 cm. to the left of the midclavicular line in the fifth intercostal space; there was a Grade 2 aortic and apical systolic murmur; the liver edge was palpable 2 fingerbreadths below the costal margin; the spleen was not felt; rectal examination showed good sphincter tone. Neurological examination revealed markedly depressed ankle jerks and diminution of vibratory sensation. The peripheral pulses were palpable but markedly diminished in the feet.

At this stage of her illness a diagnosis of diabetic neuropathy was made, and the patient was treated intensively with vitamins administered parenterally. However, the pain became increasingly severe, and movement involving the back became more and more difficult, with progressive incapacitation. She was therefore reevaluated three months after the onset of the present illness. Local examination now revealed marked paraspinal muscle spasm in the lumbar region. The Achilles reflexes were markedly diminished. Aside from diminution of vibratory sensation, there were no sensory changes. The patient turned from the prone to the supine position only with great difficulty because of pain in the low back region. The straight-leg-raising test showed limitation to about 90 degrees. Plantar responses were normal. The patient could walk only with the aid of a cane.

Laboratory investigation revealed hemoglobin 12 gm. per 100 cc.; white blood cell count, 12,600 per cubic millimeter, with a normal differential; sternal marrow examination showed no evidence of myeloma or metastatic carcinoma; urine specific gravity, 1.105, with no albumin and minimal glycosuria; stool guaiac test, negative; blood urea nitrogen, 12 mg. per 100 cc.; fasting blood sugar, 206 mg. per 100 cc.; calcium 9.4, mg. per 100 cc.; phosphorus, 3.8 mg. per 100 cc.; alkaline phosphatase, 9.2 King-Armstrong units; cholesterol, 325 mg. per 100 cc.; ester, 247 mg. per 100 cc.; total protein, 7.5 gm. per 100 cc., with albumin 4.8 gm. and globulin 2.7 gm. X-ray of the chest showed the heart to be enlarged to the left, with an elongated and tortuous aorta. X-ray of the skull was negative; x-ray examination of the lumbar spine and pelvis showed marked osteoporosis of the bones of the spine, with compression of the body of the third and fourth lumbar vertebrae (Fig. 2). In addition, there was calcification of the aorta anterior to the lumbar spine. Electrocardiogram indicated hypertrophy of the left ventricle, with involvement of the ventricular muscle.

The diagnosis of senile osteoporosis with compression of the lumbar spine was now obvious. The patient was treated with hormonal therapy and the use of a Knight spinal-brace support. She did very well on this regimen until six months later, when there was a recurrence of pain in the low back region. X-ray at this time showed a compression fracture of the 12th dorsal vertebra in addition to the involvement of the 3d and 4th lumbar vertebrae.

Fig. 2.—X-ray of the lumbar spine, Case 2, showing marked osteoporosis and compression of vertebrae.

Repetition of the laboratory investigation revealed no essential change in the findings, and repeated search for metastases via bone survey revealed no evidence of this. The patient was again treated with rest, hormones, and back support. Again, she did very well until the onset of an acute myocardial infarction. Immediately following this episode she went into acute congestive heart failure, further complicated by a cerebral vascular thrombosis, which led to her death approximately two years following the initial onset of bone symptoms.

Comment.—This case illustrates the confusion of diabetic neuropathy with osteoporosis and collapse of lumbar vertebrae. The gradual onset of pain, with its bilateral radiation, the marked diminution of ankle jerks, and the diminution of vibratory sensation, led to the initial diagnosis of diabetic neuropathy. It was only after the pain became acute and the incapacitation severe that the necessary studies were performed leading to the correct diagnosis. Subsequent specific therapy resulted in marked symptomatic and objective relief to this patient.

CASE 3.—This 58-year-old Negro man was admitted to the neurological service of the Mount Sinai Hospital because of left foot weakness of three weeks' duration. Diabetes had been discovered eight months previously, with the classical onset of polyuria, polydipsia, and weight loss. He had been treated with isophane (NPH) insulin, 25 units daily, but control was poorly maintained, with the frequent presence of acetonuria. One month prior to admission he developed acute tonsillitis associated with vomiting and resulting in severe ketosis, for which he was treated at another hospital. At the time of discharge from that hospital, he was taking isophane insulin, 100 units each morning, but still had marked glycosuria.

Three weeks before admission he experienced difficulty in raising his left foot from the ground. This was followed by stumbling and dragging of his left foot and accompanied by pain in the left calf, described as shooting and burning in character. He also complained of numbness and "pins and needles" sensation in his left big toe. Throughout this period there was poor diabetic control and continued weight loss. His physician made the diagnosis of diabetic neuropathy and referred him to the hospital for therapy.

On examination he was well developed but showed evidence of recent weight loss. His temperature was normal; blood pressure, 110/60; fundi showed no hemorrhages or exudates; the systemic examination revealed no essential abnormalities. The neurological examination showed all the cranial nerves to be intact. On walking, he lifted his entire left leg to avoid the consequence of dropping it. Motor power throughout was good except for the left foot, which showed weakness of dorsiflexion. There was also weakness of dorsiflexion of the left toe. Tendon reflexes were present and equal bilaterally except for the ankle jerks, which were bilaterally absent. There were no pathological reflexes. Sensory examination showed decreased touch sensation of the left big toe and normal position sense; vibratory sense was decreased in the left iliac crest and below the left knee and absent on the left ankle and toes; pin prick was diminished over the dorsum of the left first through fourth toes and on the plantar surface of the left big toe.

Laboratory examination showed a hemoglobin value of 12.4 gm. per 100 cc.; white blood cell count, 5300 per cubic millimeter, with normal differential; blood urea nitrogen, 11 mg. per 100 cc.; total protein, 7.1 gm. per 100 cc., with

Fig. 3.—Myelogram, Case 3. A defect in the iophendylate column is present at the level of the fourth and fifth lumbar vertebrae on the left side.

albumin, 4.3 gm. and globulin 2.8 gm.; cholesterol, 290 mg. per 100 cc.; blood amylase, 10 units; sedimentation rate, 13 mm.; fasting blood sugar, 189 mg. per 100 cc. X-rays of the chest, abdomen, and lumbosacral spine were all negative, except for the presence of vessel calcification in the pelvis. Lumbar puncture revealed normal manometric readings, negative serology, and total protein of 37 mg. per 100 cc.

In view of the poor diabetic control, the weight loss, the nature of the pain, the precipitation of symptoms following ketosis, and the bilateral absence of ankle jerks, the admitting and working diagnosis was diabetic neuropathy. At rest the sensory findings gradually regressed, but two weeks after admission it was noticed that there was progression of motor findings, with weakness of all muscle groups in the left lower extremities. His sensory and motor findings now corresponded to the distribution of the fourth lumbar level. Therefore, a myelogram was performed, which revealed the presence of a defect in the iophendylate (Pantopaque) column at the level of the fourth and fifth lumbar vertebrae on the left side (Fig. 3). In view of this, traction was instituted, using 20 lb. of weight. There was progressive improvement in sensory and motor findings. He was then fitted with a support type corset for the lumbar region. At the time of discharge there was only slight weakness of dorsiflexion of the left foot and left big toe. His diabetic status was controlled with diet plus isophane insulin, 145 units each morning. Follow-up examination three months later showed complete resolution of the foot drop, but continued absence of both ankle jerks.

Comment.—The background of poor control of the diabetes, the onset after severe ketosis, peripheral neuropathy, and the bilateral absence of ankle jerks, led directly to the diagnosis of diabetic neuropathy. Clues suggesting the correct diagnosis were (1) the suspicious unilaterality which, though not incompatible with diabetic neuropathy, is somewhat unusual; (2) the normal spinal fluid protein; (3) the sensory findings corresponding to the distribution of one nerve root, and (4) the progressive muscular involvement in the face of sensory regression. It was felt he probably had an asymptomatic mild diabetic neuropathy. However, the predominant clinical picture which was eventually established was that of a disk lesion. The proper diagnosis resulted in institution of specific therapy and produced a most salutary result.

CASE 4.*—This 57-year-old white man with known diabetes of seven years' duration was referred with a diagnosis of acute diabetic neuropathy. He was well until three weeks prior to admission, when he developed excruciating pain in the low back and left hip region, soon followed by pain in the right hip area. Associated with this was a 30 lb. weight loss. A diagnosis of diabetic neuropathy was made by his local physician. During this three week period, he was treated with thiamine and cyanocobalamin (vitamins B_1 and B_{12}) in huge doses parenterally, but because of progression of symptoms he was admitted to the Mount Sinai Hospital.

On examination he appeared chronically ill and was febrile; blood pressure, 120/80; examination of the fundi revealed no abnormalities; heart, lungs, and abdominal examination, normal; examination of the spine showed marked spasm of the lumbosacral muscles and tenderness over the fourth and fifth lumbar vertebrae. His urine was

* This case is presented with the permission of Dr. David Adlersberg.

normal except for the presence of glycosuria; hemoglobin, 12 gm. per 100 cc.; white blood cell count, 4600 per cubic millimeter, with 85% polymorphonuclear leukocytes; blood urea nitrogen, 16 mg. per 100 cc.; total protein, 7.3 gm. per 100 cc., with albumin 4.3 gm. and globulin 3.0 gm.; cholesterol, 163 mg. per 100 cc.; blood amylase, 110 units; fasting blood sugar, 158 mg. per 100 cc.; calcium, 9.5 mg. per 100 cc.; phosphorus, 3.7 mg. per 100 cc.; alkaline phosphatase, 14 King-Armstrong units; acid phosphatase, 1.6 units; sedimentation rate, 82 mm. in one hour. X-rays of the skull and skeletal system were negative except for an area of narrowing between the third and fourth lumbar vertebrae. He was discharged with no definite diagnosis, but the most likely suspicion was the presence of a metastatic process involving the lumbar vertebrae. During his first admission his diabetes was well controlled with 30 units of lente insulin daily.

Because of progressively increasing pain in the lumbar spine, continued weight loss, and an episode of acute epistaxis, he was readmitted to the hospital. The epistaxis was found to be coming from an actively bleeding vessel, which responded to cauterization. Examination and laboratory findings were the same as on the first admission except for the x-ray of the lumbosacral spine. This x-ray now revealed marked changes in the lumbar vertebrae, with evidence of a lytic process and marked narrowing of the interspaces of the third and fourth vertebrae, with calcium deposits in the surrounding soft tissue. Two bone biopsy specimens from this area revealed no sign of histological changes, but culture of this material grew out hemolytic Staphylococcus aureus. It was now felt that he had either a pyogenic bone involvement or tuberculous spondylitis and that metastatic neoplasm could still not be ruled out entirely. He was therefore treated with x-ray therapy, antibiotics, iproniazid (Marsilid), and corticosteriods. He made a dramatic response and in the next four months gained 50 lb. in weight.

He was readmitted for a third time because of some edema of the lower extremities as well as to reevaluate the status of his back. Laboratory findings were all within normal limits and approximated those on admission, except that the sedimentation rate had fallen to 30 mm.; the hemoglobin had increased to 14.5 gm. per 100 cc.; the white blood cell count was 5600, with 60% polymorphonuclear leukocytes, and the cholesterol was now 240 mg. per 100 cc. X-ray examination of the lumbosacral spine now revealed healing of the involved area, with marked calcification (Fig. 4). It was felt that in retrospect the most likely diagnosis here was pyogenic involvement of the spine.

Fig. 4.—X-ray of the lumbosacral spine, Case 4. Note the presence of destruction and secondary healing with calcification.

Comment.—The sudden onset of pain in the low back with a tendency toward bilateral radiation into the lower extremities in a known diabetic led his physician to make a diagnosis of diabetic neuropathy and institute treatment in this direction. Only further investigation and observation served to establish other pathology, which led to the necessary therapy and a most dramatic and satisfactory result.

Case 5.—This was a 59-year-old white man who was known to have had diabetes for seven years. His chief complaint was pain in the right lower extremity, beginning at the level of the hip and radiating downward. The pain was described as burning. He soon developed an associated "pins and needles" sensation in the sole of the right foot. The pain progressively increased in severity and was then described as "achey" in character. Past history included an episode of hematuria associated with the passage of a renal calculus and a fracture of the right humerus 40 years ago which healed without complication. Family history revealed that his father was a diabetic

Fig. 5.—X-ray of right femur and pelvis, Case 5, showing Paget's disease involving the femur, ischium, pubis, and ilium.

who died at the age of 80 and that a brother had diabetes and Paget's disease of the right ilium.

On examination he appeared well developed and well nourished, looking younger than his stated years. Pupils and fundi were normal, with no evidence of diabetic retinopathy. The heart was not enlarged; sounds were of good quality; blood pressure, 140/90; the prostate was smooth and unenlarged; neurological examination, which had been entirely normal two years previously, now revealed the absence of knee jerks and ankle jerks bilaterally. The peripheral pulses were normal. Laboratory examination showed normal urine and blood cell count; sedimentation rate 22 mm. in one hour; calcium, 9.0 mg. per 100 cc.; phosphorus, 3.6 mg. per 100 cc.; alkaline phosphatase, 15.2 King-Armstrong units; acid phosphatase, 1.5 units. X-ray examination of the pelvis and right femur showed Paget's disease involving the right femur, right ischium, pubis, and ilium (Fig. 5). The site of the original fracture showed no change.

At the onset he had been treated for diabetic neuropathy for a period of three months on the basis of the absent deep tendon reflexes in both lower extremities and the nature and distribution of the pain. Because of the progressive increase in the severity of the pain and beginning incapacitation, the x-ray and blood chemistry studies as related above were done. The patient visited the Lahey and Joslin clinics for further evaluation and therapy. At these institutions similar physical and x-ray findings were recorded. In addition a lumbar puncture was performed which was normal in all respects except for an elevation of the total spinal fluid protein to 62 mg. per 100 cc. The discharge diagnosis was diabetic neuritis and incidental presence of Paget's disease. On return to his home he rapidly deteriorated, with marked increase in pain, and shortly developed the classical clinical picture and the manifestations of Paget's sarcomatosis, which led to his death.

Comment.—It seems clearly established that this man had a diabetic neuropathy as manifested by the bilateral absence of deep reflexes in both lower extremities and elevation of the spinal fluid protein. However, it is equally clear that the predominant part of this picture was due to Paget's disease and its sarcomatous changes, which resulted in the death of the patient. The case illustrates the fact that diabetic neuropathy may well be simultaneously accompanied by unrelated pathological processes which can readily be masked. One must be constantly on the alert to explore any findings that are in any degree atypical.

CASE 6.—This was the first Mount Sinai Hospital admission of a 49-year-old white male cab driver complaining of visual, motor, and equilibratory difficulty. Three weeks prior to entry he noticed that he was unable to see out of the sides of his eyes without turning his head, "as though he were wearing blinders." Next morning he awoke feeling unsteady on his feet and unable to see well. There was progressive increase in his unsteadiness. He developed a high-stepping staggering gait and diplopia on looking to the right. He continued to drive his cab, but he had difficulty in focusing and had to drive with one eye closed. The legs became progressively weaker; the eyelids, half closed, and the staggering, so marked that he was hospitalized in another institution. While there he developed difficulty in holding up his neck, although respiration and swallowing were not impaired. He soon thereafter developed a nasal quality to his speech and an inability to whistle. He also experienced a sensation of coldness in his arms and legs; all four extremities became progressively weaker. At this point he was transferred to the Mount Sinai Hospital.

His past history included the fact that he was a known diabetic of 10 years' duration, well controlled on diet prior to his present illness. Since the present episode he had been given 10 to 15 units of insulin every morning. The family history included the fact that his father was a diabetic.

On examination he did not appear acutely ill; blood pressure, 165/100; temperature, pulse, and respirations were normal; lungs were clear; heart, not enlarged; no abdominal organs were palpable; the peripheral pulses were all patent; the genitalia and rectum were normal. The essential abnormalities were confined to the neurological examination, which showed that he was mentally alert and clear; the face-hand test was negative; there was complete paralysis of all movement in both eyes except for slight downward movement on downward gaze bilaterally; the eyes were in midposition and could not coverge; there was no oculocephalic response; there was a bilateral ptosis; pupils were equal and reacted to light and accommodation. The gag reflexes were bilaterally depressed, and there was a nasal quality to the voice. There was right facial weakness, marked weakness of flexion of the head, and weakness of right shoulder shrugging and of the right sternomastoid muscle. In addition he had paresis of all four extremities, more marked in the lower than in the upper and more marked on the right side than the left. The muscles were flabby, and definite atrophy could be detected; but no fasciculations were seen. No deep tendon reflexes could be elicited. The plantar responses were normal. Vibratory sensation was absent from the clavicles down.

Laboratory findings showed the urine to have a specific gravity of 1.018, 2+ albumin, and 4+ sugar; hemoglobin, 14 gm. per 100 cc.; white blood cell count, 11,100 per cubic millimeter, with normal differential; erythrocyte sedimentation rate, 98 mm. in one hour; hematocrit, 40%; blood urea nitrogen, 27 mg. per 100 cc.; fasting blood sugar, 203 mg. per 100 cc.; total protein, 6.9 gm. per 100 cc., with albumin, 3.7 gm. and globulin 3.2 gm.; cholesterol, 218 mg. per 100 cc.; blood Wassermann was negative. Five lumbar punctures during the next four weeks all showed normal pressure, with clear colorless fluid and complete absence of cells. The spinal fluid protein, which was originally 300 mg. per 100 cc., slowly fell to 88 mg. Spinal fluid serology was negative. Cultures of spinal fluid for bacteria, fungi, and acid-fast bacilli, as well as guinea pig inoculation, were negative. Electroencephalogram was normal; skull x-ray was nonrevealing, and chest x-ray was normal.

Prior to admission to Mount Sinai Hospital the differential diagnosis rested between diabetic neuropathy and a progressive vascular lesion. On admission to the Mount Sinai Hospital the possibility of diabetic neuropathy was strongly considered in view of the albuminocytological dissociation, the symmetrical paresis, and the eye signs.

The course was afebrile throughout. There was no change in the condition the first few weeks, but thereafter there was evidence of continued improvement in muscle strength, eye movements, coordination, and vibratory sensation. At the time of discharge, after a course of physical therapy, he had in great measure recovered.

Comment.—In retrospect, the fairly sudden onset, the widespread involvement, and the rather prompt recovery in the face of a high spinal fluid protein made the diagnosis of Guillain-Barré syndrome most likely. The difficulty of initially differentiating this from an acute onset of diabetic neuropathy with involvement of the brain stem is equally apparent, since all these findings occur in diabetes and the elevation of spinal fluid protein in the absence of cellular reaction is entirely compatible.

CASE 7.—This 50-year-old white woman was admitted with a history of pain in the left lower quadrant, radiating to the left gluteal muscle and down the left leg to the ankle. This pain had been becoming progressively worse, requiring meperidine (Demerol) for relief. The pain was described as being burning and occurring chiefly at night and in the early morning. The past history was significant in that she was a known diabetic of two years' duration. At the time of discovery of the diabetes she had been controlled with 10 units of protamine zinc insulin daily, but for the past year and a half she had not been taking any insulin or paying any attention to her diabetes. In addition she had known cardiac disease for the past five years, requiring digitalis and meralluride for control of congestive heart failure.

On examination she was a well-developed well-nourished woman, complaining of left-sided pain. Blood pressure was 210/150; temperature, pulse, and respirations were normal; thyroid, normal; skin showed moderate psoriasis; heart was enlarged to the left, with the point of maximal impulse in the anterior axillary line; the second pulmonic sound was louder than the second aortic sound; the fundi showed narrowing of the vessels, but no hemorrhage or exudates were present; cranial nerves were intact; the left ankle jerk was diminished; there was pain on the straight-leg-raising test on the left; there was tenderness of both calves, the left being more marked than the right.

Laboratory findings showed the urine normal in all respects except for glycosuria; hemoglobin, 14 gm. per 100 cc.; white blood cell count, 6800 per cubic millimeter, with a normal differential; sedimentation rate, 20 mm. in one hour; blood urea nitrogen, 10 mg. per 100 cc.; fasting blood sugar, 125 mg. per 100 cc.; total protein, 6.8 gm.

per 100 cc., with albumin 3.9 gm. and globulin 2.9 gm.; calcium, 10.1 gm. per 100 cc.; phosphorus, 3.2 mg. per 100 cc.; alkaline phosphatase, 8 King-Armstrong units; cholesterol, 224 mg. per 100 cc.; blood serology, negative. Lumbar puncture revealed normal manometrics, with total protein 38 mg. per 100 cc.; spinal fluid serology and collodial gold were negative; bone marrow, negative. Electrocardiogram was interpreted as showing left ventricular hypertrophy with ventricular muscle involvement. X-ray of the chest showed the heart enlarged to the right and left. X-ray of the lumbosacral spine, pelvis, and hips revealed no abnormalities in the bones, but there was calcification of the lumbar aorta and of the splenic artery.

She was sent to the hopsital with a diagnosis of diabetic neuropathy for control of pain. The diagnosis was originally based on the fact that the pain was in the lower extremities; it was aggravated at night, and the patient had ignored her diabetic state. Because of the localization of the pain and its suggestive distribution, myelography was performed. This showed a typical disk deformity at the level of the fifth lumbar and first sacral levels on the left side. The patient was treated for a herniated disk and made a slow but satisfactory recovery.

Comment.—The neurological picture after more careful evaluation was not that of diabetic neuropathy, as evidenced by normal sensory neurological findings, normal spinal fluid proteins, the unilaterality of the lesion, and, of course, the unequivocal evidence of a filling defect on myelography. Appropriate therapy produced beneficial results.

Comment

It would appear from the foregoing that mimicry of diabetic neuropathy by coincidentally occurring pathology not specifically related to diabetes is not unusual. The reverse, namely, mimicry of many disease patterns by diabetic neuropathy, has frequently been recorded. How can this problem be resolved?

At the present time, in view of the absence of any symptoms, signs, or laboratory findings pathognomonic of diabetic neuropathy, extreme caution must be exercised in diagnosis. The appearance of neurological abnormalities in a diabetic must perforce immediately suggest the diagnosis of diabetic neuropathy. Nevertheless, regardless of the frequency of this complication and the statistical probability of such diagnosis being correct, it should always be made with reservation. The diagnosis of diabetic neuropathy may be made only after the complete exclusion of any and all other possible explanations. If this be accomplished, then one may be more secure if the spinal fluid total protein is elevated and the course of the syndrome remains compatible with known experience.

The definitive clarification of the diagnostic dilemma will not, in all probability, be reached via the strictly clinical approach. A more likely road to the goal of a pathognomonic feature may well lie in a further study of the spinal fluid abnormalities. It has long been recognized that in patients with diabetic neuropathy there is usually an elevation of the total protein content of the spinal fluid. The nature of this protein elevation, which protein fractions are involved, or whether there are abnormal proteins are problems currently under investigation. It is hoped that such studies will help clarify a confused situation.

Summary

Representative case histories are presented indicating pitfalls in the diagnosis of diabetic neuropathy.

The diagnosis of diabetic neuropathy must, at present, be based on the exclusion of all other possible explanations. It may be corroborated by the presence of increased spinal fluid total protein and by the clinical course.

45 E. 66th St. (21).

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Auricular Fibrillation

Report on a Study of a Familial Tendency, 1920-1956

WILLIAM L. GOULD, M.D., Albany, N. Y.

In 1891 a young Jewish tailor, Case 4,* emigrated to this country from Russia with his wife and began the prologue to a unique chapter in medical history. This young man settled in Albany, N. Y., established himself as a tailor, fathered a family of five children, and later helped to bring his parents and 10 sisters and brothers from Russia. These few facts about this person seem typical enough of the 19th-century immigrant, but he is of particular importance from the physician's viewpoint because he is the keystone of a continuing 36-year study of a familial tendency toward auricular fibrillation.

The Study

A survey of all the medical literature on this subject produced descriptions of occurrences of auricular fibrillation among only two families,[1,2] both dealing with males within one generation—the first three brothers and the second two brothers. This study now being reported of 113 males and females not only provides basic information about auricular fibrillation but also sheds new light on possible causes, diagnosis, and treatment of the condition.

Observation of Case 1 and five generations of his family revealed that of the 41 members of this family who lived to the age of 40, there were 21 with fibrillation. In 9 of the 22 cases who went into their seventh decade the condition became perpetual. Many of those just entering their fifth or sixth decade are developing fibrillation as this is being written. One person, Case 4, had a fibrillation for 38 years with no signs of decompensation at any time. Usually when the fibrillation becomes perpetual the symptoms associated with the paroxysmal fibrillation diminish. As a matter of fact, Case 4 walked about at the age of 94 with his usual swift gait and had no subjective symptoms of the irregularity for over 15 years except with mental or physical stresses. Nevertheless, his electrocardiogram revealed a perpetual auricular fibrillation. The last two of the five generations are too young to produce much information for the study at present but are being followed carefully for early symptoms. Case 38, at the age of 32, is the first one of the fourth generation to have started the attacks of paroxysmal fibrillation. As a matter of fact, as far as is known he is the youngest one in this family ever to have started fibrillating. Traits of children and grandchildren through marriage of the principals may be influencing factors which are not evaluated in this study.

Diagnosis

Diagnosis of these cases of paroxysmal auricular fibrillation often presents many

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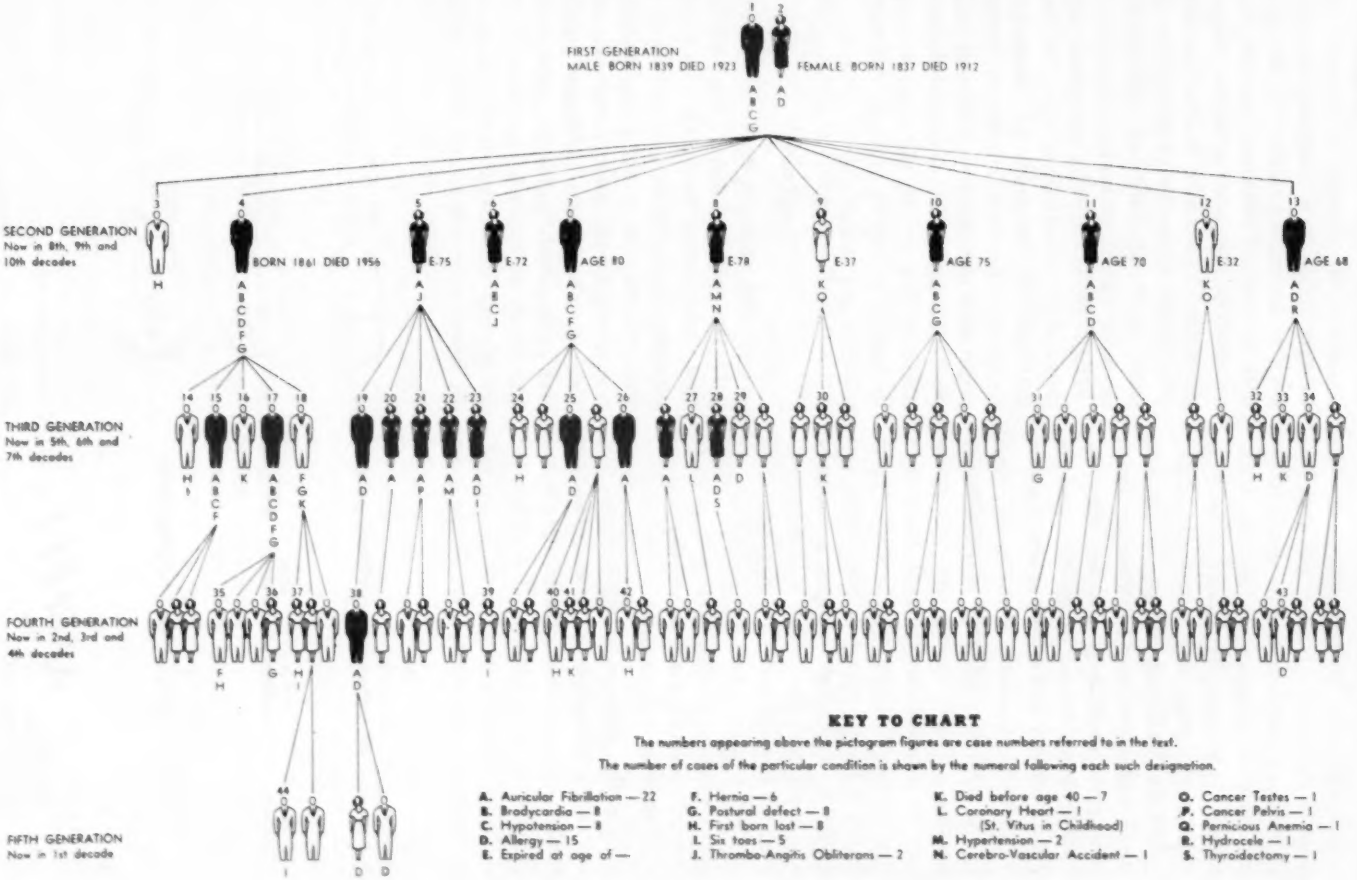
Chief of Staff, Jewish Home and Hospital for Aged, Troy, N. Y.

* Case numbers refer to pictograms on Figure 1.

Fig. 1.—The original couple shown as the first generation were stepbrother and stepsister. The period of time of the family tree ranges from 1837 to the present date. The family tree consists of 57 males and 56 females in five generations. Only four of the many great-great-grandchildren in the fifth generation are depicted. Those with auricular fibrillation are noted as solid pictogram figures. These include 10 men and 12 women, for a total of 22. In the first and second generations all who lived to the sixth decade and beyond developed auricular fibrillation. In the third generation cases of auricular fibrillations are developing from time to time, with the youngest ones, at the moment, unaffected. The youngest case of fibrillation is Case 38, aged 32, in the fourth generation. Projecting the above, how many in this family may eventually develop auricular fibrillation is anyone's guess. Changes are constantly occurring.

FAMILIAL AURICULAR FIBRILLATION IN FOUR GENERATIONS



KEY TO CHART

The numbers appearing above the pictogram figures are case numbers referred to in the text.

The number of cases of the particular condition is shown by the numeral following each such designation.

- **A.** Auricular Fibrillation — 22
- **B.** Bradycardia — 8
- **C.** Hypotension — 8
- **D.** Allergy — 15
- **E.** Expired at age of —
- **F.** Hernia — 6
- **G.** Postural defect — 8
- **H.** First born last — 8
- **I.** Six toes — 5
- **J.** Thrombo-Angitis Obliterans — 2
- **K.** Died before age 40 — 7
- **L.** Coronary Heart — 1 (St. Vitus in Childhood)
- **M.** Hypertension — 2
- **N.** Cerebro-Vascular Accident — 1
- **O.** Cancer Testes — 1
- **P.** Cancer Pelvis — 1
- **Q.** Pernicious Anemia — 1
- **R.** Hydrocele — 1
- **S.** Thyroidectomy — 1

problems to the physician. The usual symptoms—palpitation; the irregular beat; "the heart in the mouth" feeling; the weakness, dizziness, or faintness, and the cold sweat—are likely to disappear before the doctor arrives. It is especially difficult in the early stages, for it may be a matter of seconds before the fibrillation passes. By the time the physician arrives and listen to the heart, nothing extraordinary can be observed. Cardiograms show no irregularity, and the blood chemistry and urinalysis are negative.

One of the members of the family, Case 4, had extreme difficulty in obtaining a diagnosis. Every appropriate means was used to pinpoint the cause of his attacks of weakness, dizziness, and faintness. Even during a 10-day period of observation and testing in a hospital no heart irregularity was noted, and the patient was discharged from the hospital without a diagnosis. Only two years later, when the attacks became more pronounced, was fibrillation actually detected. Eleven years after the original attack it became perpetual.

Since the paroxysmal attack is at first momentary and obviously passes quickly, the problem in such nondiagnosed cases is not so much one of treatment but is rather one of the psychological effect upon the patient. In many cases functional heart disease is the diagnosis, or, with a "no diagnosis" announced to the patient, he becomes overwrought, thinks he is imagining things, and worries disproportionately. Until further tests are devised, however, detection of the auricular fibrillation in its earlier stages is sometimes impossible. Since the knowledge of a familial tendency may be an aid to diagnosis, the physician should include questioning along these lines in the examination.

Diagnosis of auricular fibrillation in its larger stages is simple enough. Although, as mentioned previously, symptoms often disappear when the fibrillation becomes perpetual, an electrocardiogram will readily show the irregular beat characteristics of the condition (Fig. 2). By this time the irregular heart beat may be promptly detected by palpation and auscultation.

Treatment

Treatment varies from patient to patient and is generally very simple. First and foremost in the care of the patient with familial auricular fibrillation is continuation of his daily routine. He is not a cardiac-failure patient and should not be treated as such. This type of auricular fibrillation does not even predispose the patient to cardiac failure. This study shows the importance of differentiating between a compensating and decompensating fibrillation. The patients

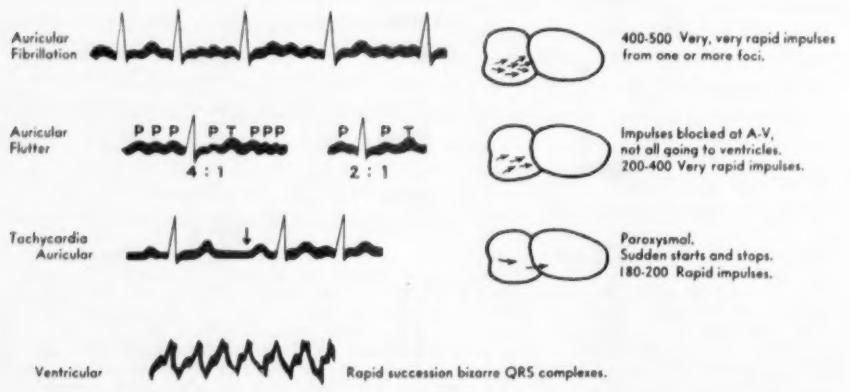

Auricular Fibrillation
400-500 Very, very rapid impulses from one or more foci.
Auricular Flutter
P P P P T P P P
4 : 1
P P T
2 : 1
Impulses blocked at A-V, not all going to ventricles. 200-400 Very rapid impulses.
Tachycardia Auricular
Paroxysmal. Sudden starts and stops. 180-200 Rapid impulses.
Ventricular
Rapid succession bizarre QRS complexes.

Fig. 2.—Electrocardiographic differences between auricular fibrillation, flutter, and tachycardia.

compensating can and do live normal life spans; those decompensating do not. Furthermore, the treatment is radically different. Among the 113 people in the study only 1, Case 27, died of a coronary attack—at the age of 40—and here there was a rheumatic history in childhood. It is interesting to note that many of these people with the fibrillation have low rather than high blood pressure. Systolic blood pressures of fibrillating patients in the study generally ranged from 102 to 160, with diastolic of 60 to 102. There were two cases, cases 8 and 32, associated with hypertension.

Two cases who left the area were hospitalized and treated as heart-failure cases. In both, the patients did not improve until those extreme precautions were stopped.

Often, particularly in the early stages, simply a postural change is all that is required to end an attack. Moving from the left to the right or sitting up in bed may stop it. Some of the severest attacks which occur during the night and keep the patient awake disappear as soon as the person gets up and moves about. This is another example of postural change but also illustrates harm that can be done by prolonged bed rest.

Some patients have fibrillations without even knowing it, while others are more aware of them. One patient who frequently experienced fibrillation found that if he stopped taking his pulse too regularly he experienced fibrillation less often. In some cases it becomes as important to educate the patient to stop taking his pulse as it is to teach some people to throw away their thermometers.

When the fibrillation is not abated by ordinary postural means, bowel evacuation for any gaseous distention, or other methods described above, the barbiturates are the drugs of choice. They appear to be far more beneficial to the patient than either digitalis or quinidine, which are usually administered. Glyceryl trinitrate (nitroglycerin) was found to be of no use in treating these cases of auricular fibrillation.

Patients should be kept in good general health and avoid excesses, such as overeating and overfatigue, when they know that this may bring about an attack. Allergic manifestations should be avoided as much as possible.

Prognosis

With correct diagnosis and proper treatment the prognosis for these patients with auricular fibrillation as seen in this study is that they will live normal healthy lives. Even with perpetual fibrillations, most lived to a ripe old age. Major dangers of this condition are misdiagnosis resulting in enforced bed rest or diagnosis which leads to overconcern and anxiety on the part of the patient.

Case Histories

These case histories are based on data collected from 1920 to 1956 and are representative of 22 cases of auricular fibrillation observed in this study, including females as well as males.

CASE 1 (1839-1923).—A man who emigrated from Russia to the United States in 1892. He had 11 children, 19 grandchildren, and 57 great-grandchildren. A diagnosis of auricular fibrillation was made when he was 81 years old, although he probably had been fibrillating for many years. At 84 he died of cardiovascular-renal disease.

CASE 4 (1861-1956).—A man who emigrated to this country in 1891 as a tailor. At the age of 52 he began getting attacks of weakness and fainting spells and broke out in cold sweats. He seemed to feel relief as soon as he sat down and drank a glass of water. These attacks were momentary at first, lasting seconds or minutes. He noticed that these attacks occurred when he was very hungry, if he skipped a meal, if he overate, or if he had gaseous distention. After having these attacks for several years without obtaining a diagnosis he was hospitalized. After a series of tests and careful observation by physicians and nurses he was discharged from the hospital without a diagnosis. Three years later, when attacks began to last several hours, the irregularity was noted and the diagnosis of paroxysmal auricular fibrillation was made. At the age of 62 the fibrillation became perpetual. He fibrillated for 38 years with never a sign of failure. His urine and blood chemistry were negative; his blood pressure was 100 to 130 systolic and 76 to 92 diastolic. Quinidine and digitalis were used only initially but did not appear to stop the fibrillation any sooner than no medication at all. Glyceryl trinitrate was also

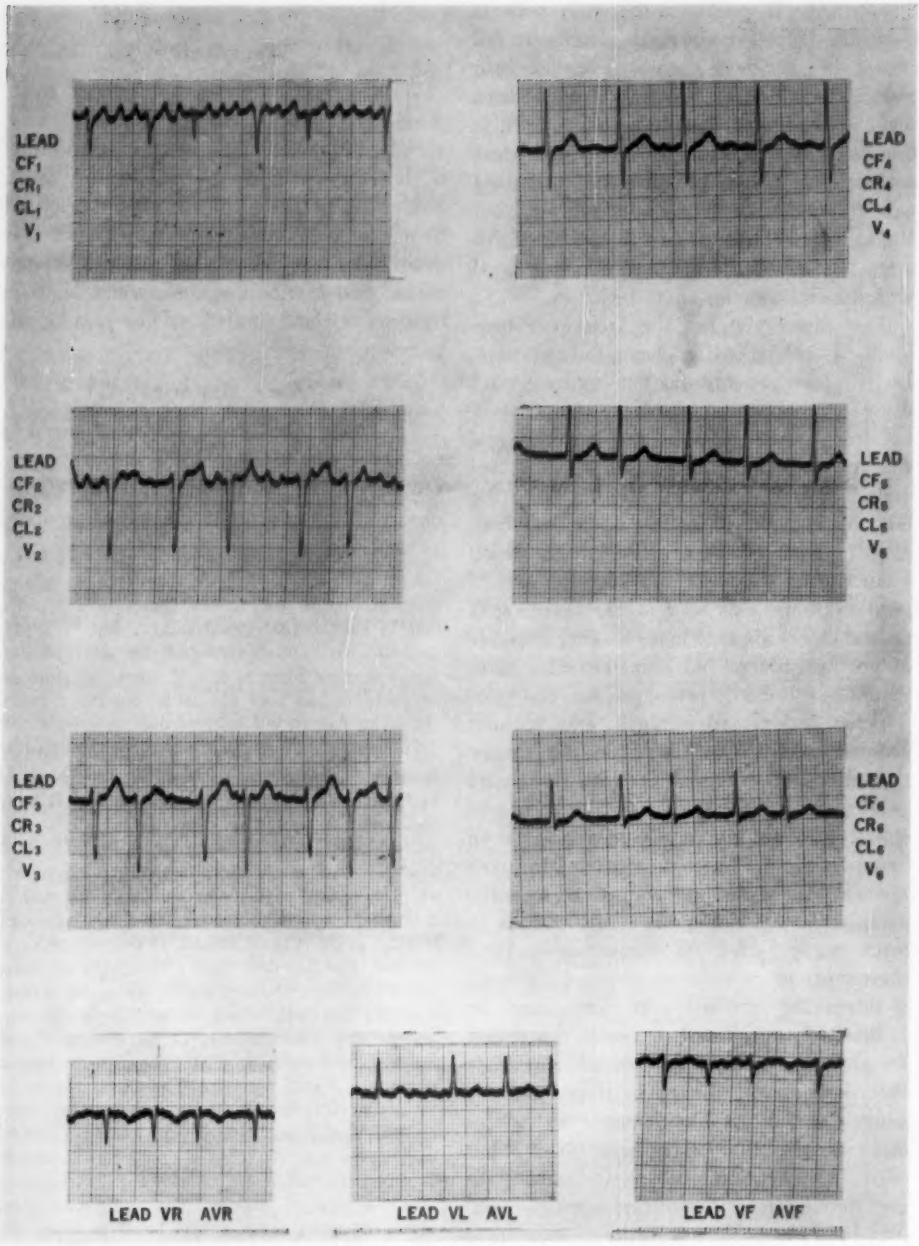

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Fig. 3.—Case 7 fibrillating.

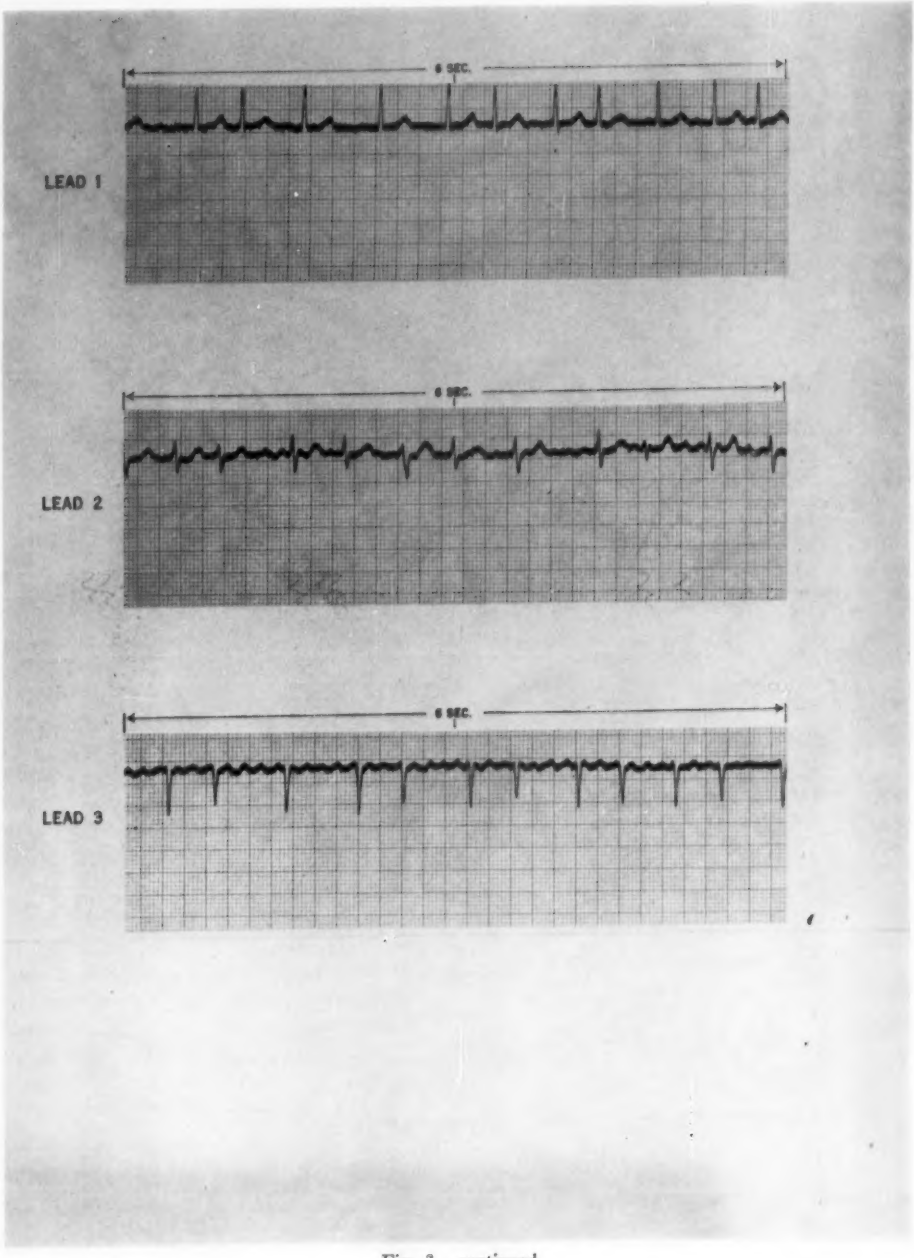

Fig. 3.—continued

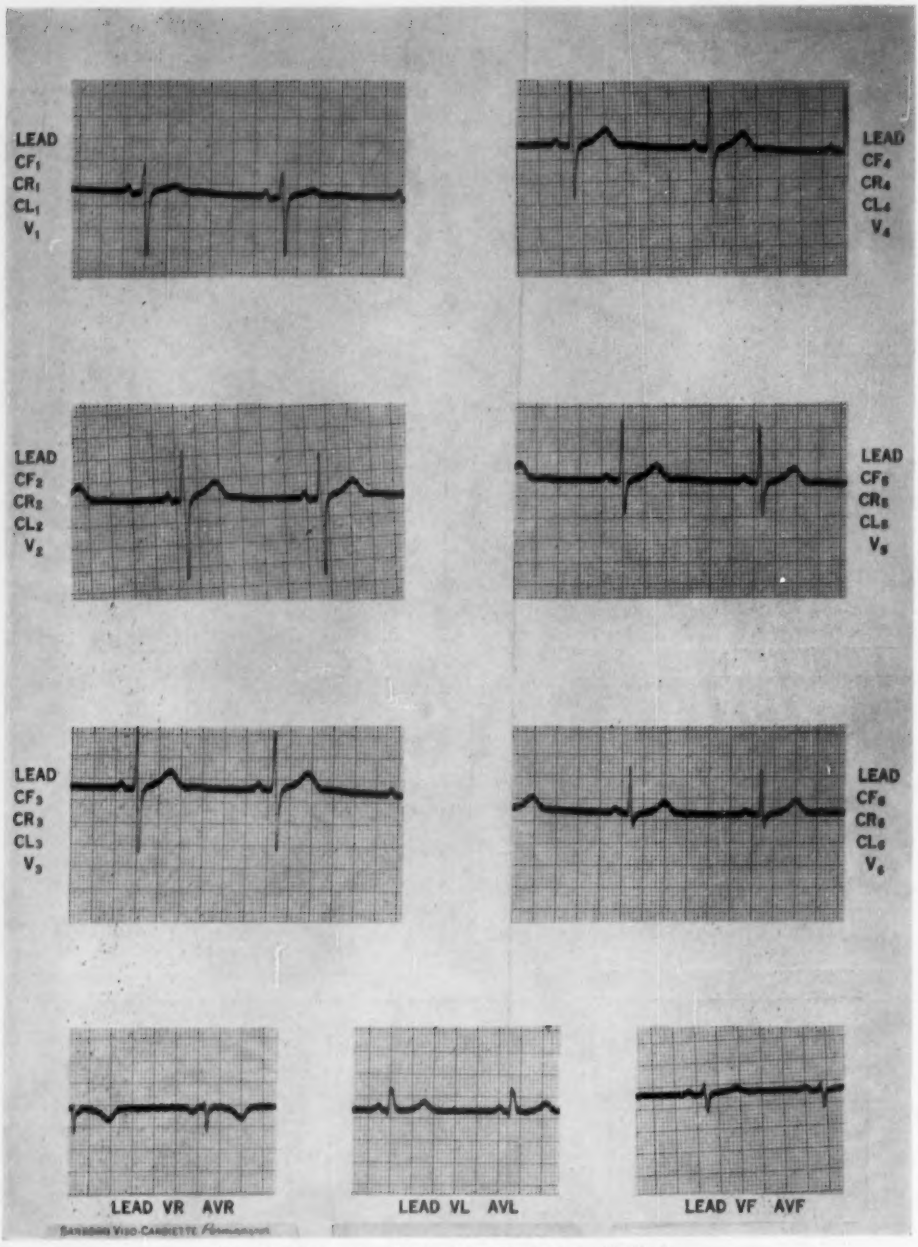
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Fig. 4.—Case 17 with bradycardia before fibrillation.

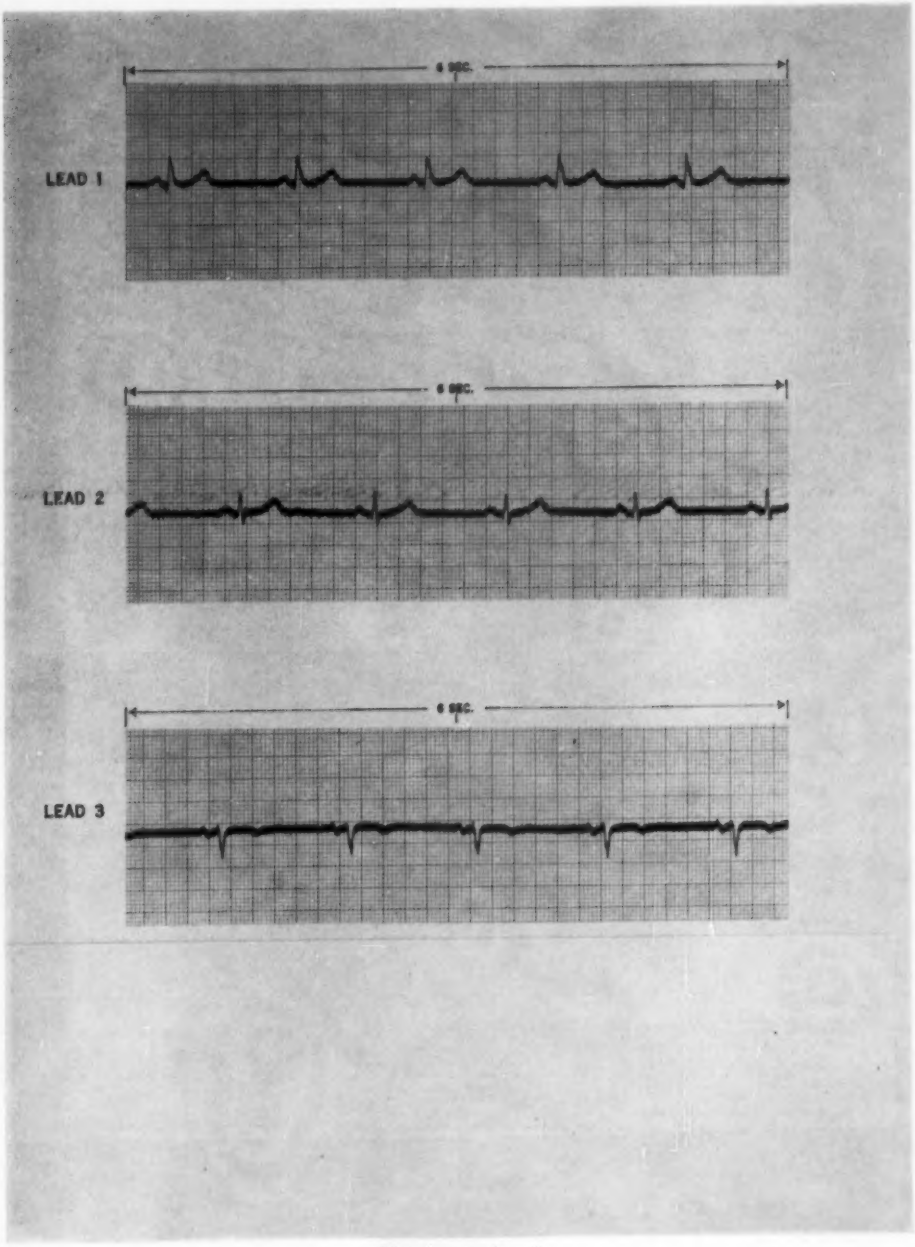
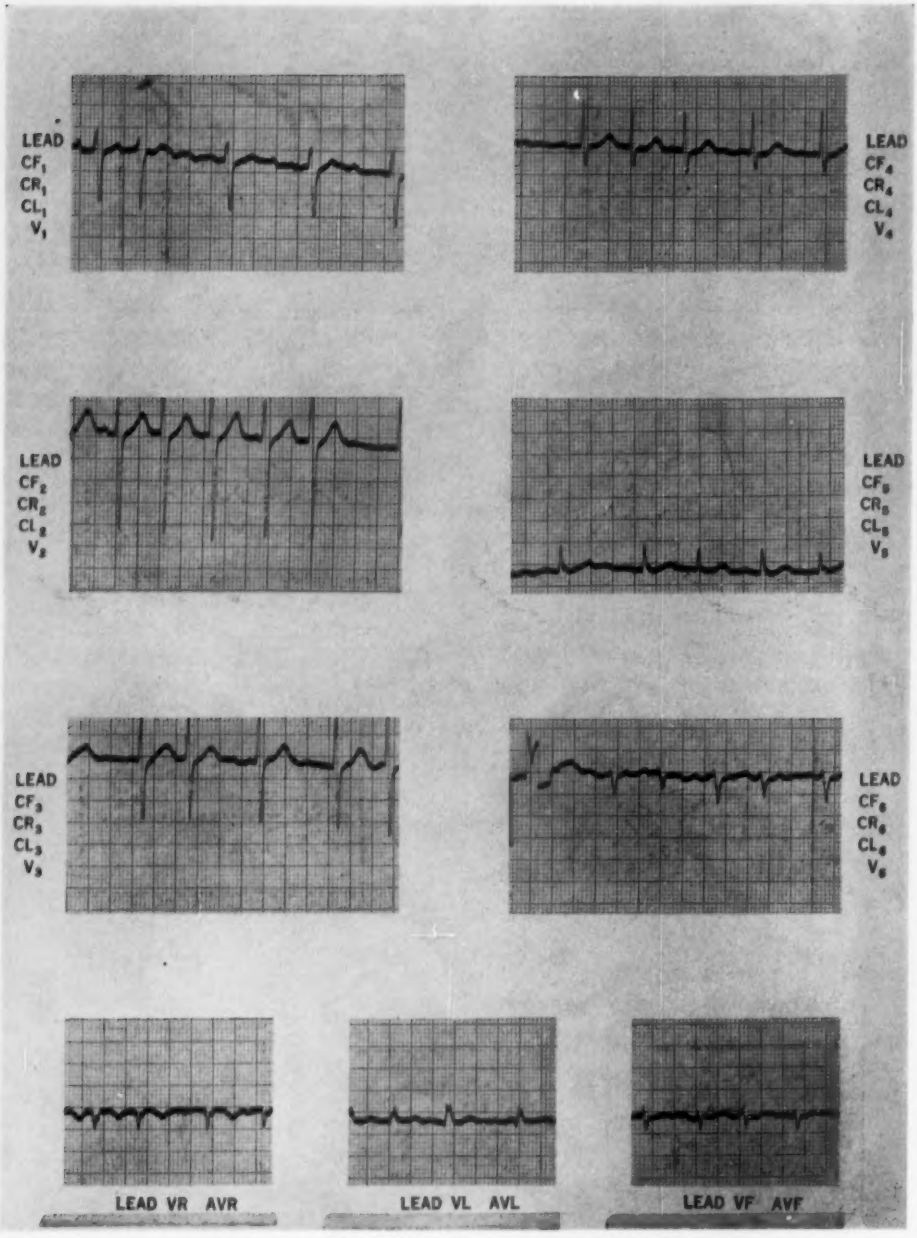


Fig. 4.—continued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LEAD CF4 CR4 CL4 V4
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Fig. 5.—Case 17 with paroxysmal auricular fibrillation.

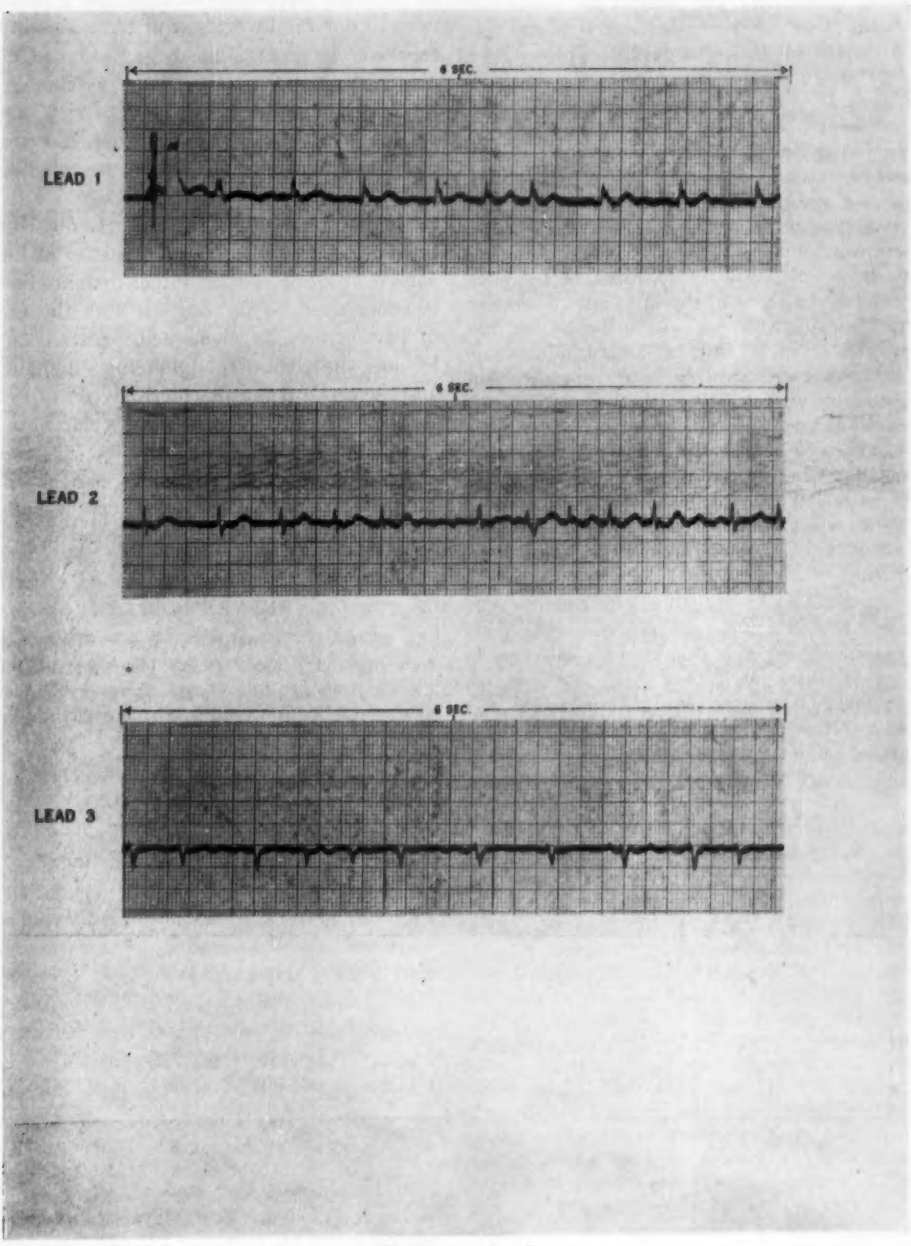

Fig. 5.—continued

tried but created considerable head disturbances, probably because of the low blood pressure. Phenobarbital in small doses seemed to alleviate the pounding sensation and shorten the paroxysmal attacks. Case 4 suddenly died several months ago, at the age of 94, having been most active until the very last moment.

CASE 17.— An attorney aged 59 saw his physician because he noticed a slight "flip-flop" with the feeling that his "heart came up in his throat" and he coughed momentarily. Dizziness and a hot or cold sweat were also manifest. Examination revealed that he had hypotension, bradycardia, and inguinal hernia and was allergic to several foods as well as dust. "Palpitations" became more frequent, lasting for several hours. Sometimes they would go away for most of the day and then reoccur at night. Attacks seemed to dissipate with morning activities. It appeared that paroxysms were definitely associated with allergic manifestations, since there was never an allergic manifestation without fibrillation. Perpetual manifestation has not yet occurred. Therapy included phenobarbital with antihistamines and avoidance of the allergic foods: onions, cheese, chocolate, and garlic. Also, injections for dust allergies were given.

CASE 7.—A man aged 80 was the oldest to start fibrillating. He began his paroxysms five years ago, exactly the same year when his sons, ages 46 and 51, began fibrillating. After one year the fibrillation became perpetual. Phenobarbital acts as a specific for his sons and himself. Figure 3 shows his electrocardiogram with fibrillation.

Summary

This report on a study tracing 22 cases of auricular fibrillation through five generations of one family deals with 113 males and females. It points out the importance of diagnosing the condition from a psychological as well as a therapeutic point of view and of the need to differentiate between the compensating and noncompensating fibrillation.

Of major importance in the treatment of this auricular fibrillation is the matter of the patient's routine. Action rather than inaction is emphasized. This, coupled with the use of barbiturates, as mentioned, generally alleviates the condition. Quinidine, digitalis, and glyceryl trinitrate (nitroglycerin), so frequently used in ordinary auricular fibrillation, are mostly not required in this familial type. The fibrillating patient receiving proper medical care can usually look forward to a normal life expectancy.

453 Western Ave.

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The Sensitivity of Two Hundred Strains of Hemolytic Staphylococcus to a Series of Antibiotics

ROBERT G. PETERSDORF, M.D.; JAMES A. CURTIN, M.D., and IVAN L. BENNETT Jr., M.D., Baltimore

Infections with antibiotic-resistant bacteria, particularly staphylococci, have become a serious problem in hospital practice. Many reports attest to the increase in frequency and mortality rate of clinical infections with this organism during the past decade. This subject has recently been reviewed in detail by Rogers.[1]

One consequence of this increase in resistant strains has been the search for additional antimicrobials to combat organisms refractory to agents presently available. A number of new drugs have been recommended for treatment of resistant staphylococcal infections. The determination of the antibiotic sensitivity of this group of organisms has become a mandatory procedure in any serious infection.

In a previous report from this laboratory, the sensitivity of 100 strains of pathogenic bacteria to 10 antibiotics was tabulated.[2] Sixty-eight of the one hundred were staphylococci, and the present report gives a detailed analysis of one hundred additional strains of this organism isolated from severe infections. An additional 100 strains of staphylococci isolated in a study designed to evaluate the routine use of chemoprophylaxis in unconscious patients[3] were compared with the 100 organisms obtained from patients with overt staphylococcal disease.

For reasons described previously,[2] a tube-dilution method with determination of both bacteriostatic and bactericidal end-points was employed in place of a "disk" method or its variants. In addition to susceptibility to antibiotics, the bacteriophage type of over half the organisms was determined. Finally, by analysis of hospital records of patients from whom these organisms were isolated, the results of these in vitro tests were correlated with clinical results.

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The Biological Division, Department of Medicine, The Johns Hopkins University School of Medicine. Research Fellow of the National Foundation for Infantile Paralysis (Dr. Petersdorf); Commonwealth Fund Fellow (Dr. Curtin); from The Johns Hopkins University (Dr. Bennett).

Materials and Methods

Organisms.—One group consisted of 100 strains of staphylococci isolated from patients in whom they were responsible for frank infections (henceforth called the "clinical" group). An additional 100 organisms were cultured from the anterior nares of patients hospitalized for cerebrovascular accidents; half of these patients were receiving or had recently been given chemotherapy. All organisms produced hemolysis on human blood agar and formed black colonies on tellurite-glycine agar (BBL*). They were not routinely differentiated into albus or aureus varieties. In addition to plating on tellurite-glycine agar, we performed coagulase tests on many strains; the results were always positive.

Antibiotic Sensitivities.—All organisms were tested against penicillin, erythromycin, tetracycline, chloramphenicol, bacitracin, neomycin, oleandomycin, (Pfizer Laboratories), novobiocin (Cathomycin, Merck & Co., Inc., and Albamycin, The Upjohn Company). Some organisms were also tested against spiramycin (Merck & Co., Inc.) and vancomycin (Eli Lilly and Company).

The organism to be assayed was grown in trypticase soy broth at 37 C for 18 hours, and an aliquot of this culture was diluted 1:1000 with broth immediately before tests were performed. This diluted inoculum was added in the amount of 0.1 ml. to each of a series of Kahn tubes containing 0.8 ml. of broth and 0.1 ml. of a stock dilution of an antibiotic. The final volume in the test system was therefore 1.0 ml., and each drug except penicillin was employed in final concentrations of 0.2, 1.0, 5.0, 10, 20, 50, and 100μg. or units per milliliter. The concentrations of penicillin

* Baltimore Biological Laboratory.

TABLE 1.—*The Sensitivity of Staphylococci from One Hundred Clinical Infections to Eleven Antibiotics*

		Concentration, μg./Ml.							
		0.2	1.0	5.0	10	20	50	100	>100
		Strains, No.							
Penicillin	Bacteriostatic	4	2	31	9	11	17	9	17
	Bactericidal	1	0	10	4	9	16	19	41
Erythromycin	Bacteriostatic	12	53	8	2	7	0	0	18
	Bactericidal	1	9	6	7	15	14	12	36
Tetracycline	Bacteriostatic	0	26	4	0	0	12	15	43
	Bactericidal	0	2	5	4	5	11	14	59
Chloramphenicol	Bacteriostatic	0	0	30	56	4	9	1	0
	Bactericidal	0	0	4	2	5	8	19	62
Bacitracin *	Bacteriostatic	1	30	52	29	5	3	0	0
	Bactericidal	0	5	21	33	12	13	14	2
Neomycin	Bacteriostatic	2	13	46	25	10	4	0	0
	Bactericidal	2	4	37	23	18	6	5	5
Oleandomycin	Bacteriostatic	0	16	65	7	1	4	4	3
	Bactericidal	0	4	4	2	5	6	17	62
Novobiocin (Cathomycin)	Bacteriostatic	33	55	10	0	2	0	0	0
	Bactericidal	3	11	6	11	10	15	22	22
Novobiocin (Albamycin)	Bacteriostatic	31	57	7	3	2	0	0	0
	Bactericidal	3	7	9	12	11	19	14	25
Spiramycin †	Bacteriostatic	0	0	4	29	29	14	3	3
	Bactericidal	0	0	0	2	5	4	7	64
Vancomycin ‡	Bacteriostatic	0	1	0	16	1	0	0	0
	Bactericidal	0	1	0	7	6	3	1	0

* Units/ml.
† 82 strains.
‡ 18 strains.

were 0.2, 0.5, 1.0, 5.0, 10, 20, 30, 40, 50, 60, 70, 80, 90, 100, and 250 units per milliliter. After incubation at 37 C for 24 hours the tubes were examined for evidence of growth. The first tube showing no turbidity was taken as the bacteriostatic endpoint. A loopful of material from all tubes that remained clear was plated on blood agar, and the first dilution from which colonies failed to grow after 24 hours at 37 C was taken as the bactericidal end-point. Stock dilutions of each antibiotic were prepared in quantity and stored at −20 C. For most tests the entire series of tubes containing broth and drugs had been prepared ahead of time and frozen at −20 C until used. Fresh stocks of antibiotics were prepared at intervals of one to two months, and each new solution was tested against a series of reference strains. In the same way frozen stocks of antibiotics were checked periodically against reference strains. In no instance was any deterioration detectable.

Bacteriophage Typing.—The methods used for propagation and titration of staphylococcal bacteriophage and for their use in typing have been described in detail by Blair and Carr.[4] The 25 standard bacteriophage strains were supplied by Dr. John E. Blair, who also checked the typing results with selected strains in this series.

TABLE 2.—*The Sensitivity of One Hundred Strains of Staphylococci from Nasal Carriers to Eleven Antibiotics*

		Concentration, μg./Ml.							
		0.2	1.0	5.0	10	20	50	100	>100
		Strains, No.							
Penicillin	Bacteriostatic	4	4	29	7	11	7	23	15
	Bactericidal	2	1	22	5	9	12	13	36
Erythromycin	Bacteriostatic	5	45	1	1	1	1	0	46
	Bactericidal	2	2	4	3	13	12	5	59
Tetracycline	Bacteriostatic	0	21	2	0	0	1	12	64
	Bactericidal	0	1	1	5	4	4	16	69
Chloramphenicol	Bacteriostatic	0	0	81	14	1	3	1	0
	Bactericidal	0	0	4	1	3	6	18	68
Bacitracin *	Bacteriostatic	0	11	61	21	4	0	3	0
	Bactericidal	0	6	29	28	12	10	8	7
Neomycin	Bacteriostatic	0	5	63	25	5	2	0	0
	Bactericidal	0	3	44	27	10	10	4	2
Oleandomycin	Bacteriostatic	0	5	66	5	1	0	0	23
	Bactericidal	0	2	1	2	3	5	16	71
Novobiocin (Cathomycin)	Bacteriostatic	16	78	5	0	0	1	0	0
	Bactericidal	0	14	10	16	15	23	15	7
Novobiocin (Albamycin)	Bacteriostatic	10	87	2	0	1	0	0	0
	Bactericidal	0	14	8	13	18	14	13	19
Spiramycin †	Bacteriostatic	0	3	24	32	0	2	0	2
	Bactericidal	0	0	1	1	4	2	6	49
Vancomycin ‡	Bacteriostatic	0	1	0	32	0	0	0	0
	Bactericidal	0	0	0	14	3	5	6	5

* Units/ml.
† 63 strains.
‡ 33 strains.

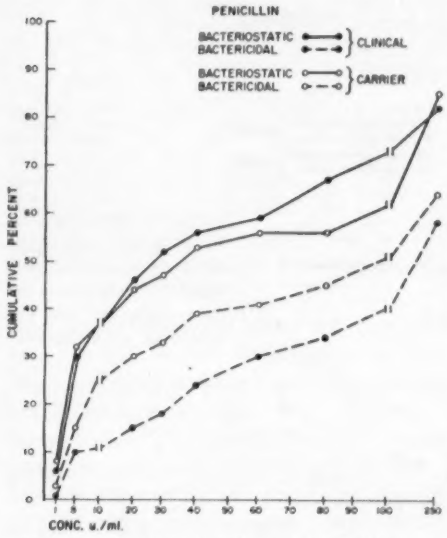

Fig. 1.—The bacteriostatic and bactericidal effect of penicillin on 100 strains of staphylococci isolated from patients with severe infections and 100 strains from hospitalized nasal carriers.

Results

In Vitro Sensitivity of Staphylococci.—The susceptibility of the 200 strains tested is summarized in Tables 1 (clinical infections) and 2 (nasal carriers). The numerator depicts the number of strains inhibited by each drug in a given concentration, and the denominator indicates the concentration found to exert a bactericidal effect. These findings are illustrated graphically in Figures 1 to 3, in which the cumulative percentages of strains in each group that were inhibited or killed are plotted against concentration of drug.

The susceptibility of the 200 strains generally paralleled that reported for staphylococci from this laboratory. In general, organisms isolated from patients with infections differed very little from those from nasal carriers. The clinical group was slightly more sensitive; this was particularly noticeable for erythromycin and oleandomycin. Many strains were inhibited by several drugs but killed by none. Penicillin, bacitracin, and neomycin, of course, were the effective bactericidal agents.

Although at first glance penicillin seemed ineffective, nearly 60% of strains were inhibited, and about 35% were killed by 50 units per milliliter of the drug (Fig. 1). This level can be achieved in vivo by high dosage intravenously combined with the use of an agent such as probenecid (Benemid), and penicillin continues to be a useful drug for staphylococcal infections.

Nearly 75% of strains from the clinical group and 50% from the carriers were in-

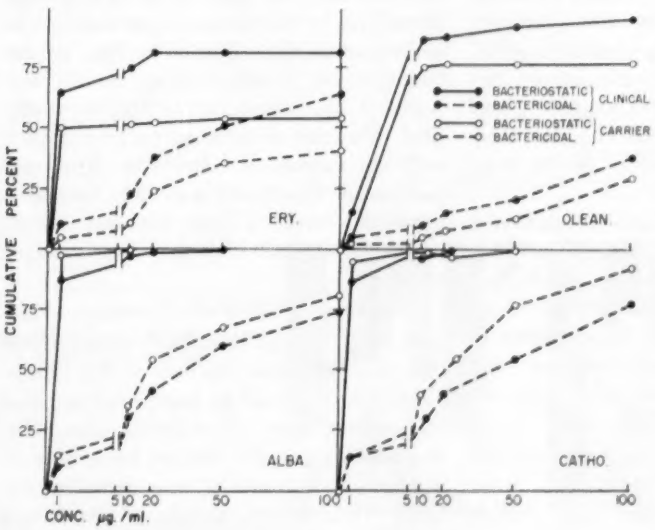

Fig. 2.—The bacteriostatic and bactericidal action of erythromycin, oleandomycin, and novobiocin (Cathomycin and Albamycin) against 100 strains of staphylococci from clinical infections and 100 from nasal carriers.

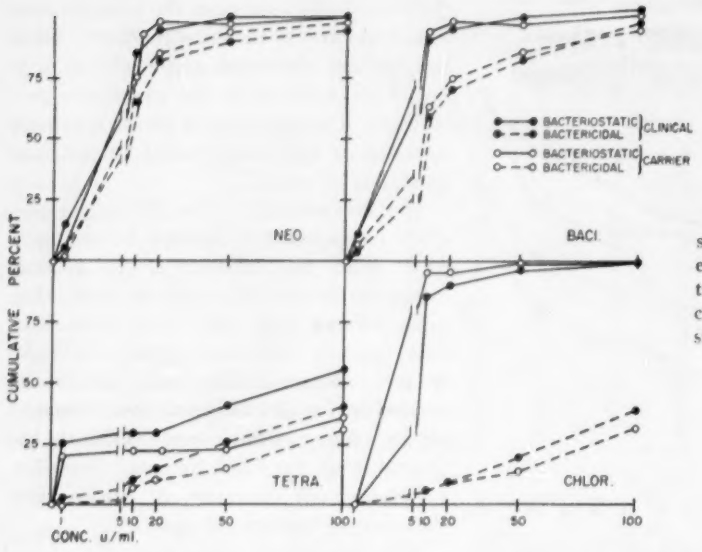

Fig. 3.—The bacteriostatic and bactericidal effect of neomycin, bacitracin, tetracycline, and chloramphenicol on 200 strains of staphylococci.

hibited by 1μg. per milliliter or less of erythromycin (Fig. 2). However, it should be emphasized that the incidence of strains resistant to this agent is increasing and, furthermore, that the drug is bactericidal for 50% of strains only in concentrations that far exceed those obtainable clinically under most circumstances.

Oleandomycin appeared to possess no particular advantage. There was a tendency for strains resistant to erythromycin to be resistant to oleandomycin also, although "cross resistance" was far from complete. This finding is of considerable interest because to date this drug has not been given to any patient in The Johns Hopkins Hospital. The bactericidal action of this drug was negligible (Fig. 2).

Two brands of novobiocin (Cathomycin and Albamycin) were employed in this series of tests (Fig. 2). The results obtained with these agents were virtually identical; novobiocin was uniformly bacteriostatic in concentrations of 1μg. per milliliter, and 50% of the strains were killed by concentrations of 20μg. per milliliter.

As has been pointed out, neomycin and bacitracin were potent bactericidal drugs. Although toxicity precludes their routine clinical use, they can be highly beneficial when employed locally, and in special instances systemic administration is indicated.

The results with tetracycline indicate striking resistance of these staphylococcal strains. Chloramphenicol, on the other hand, inhibited 90% of them in concentration of 10μg. per milliliter but showed little direct killing action.

Blood levels of greater than 1μg. to 2μg. per milliliter are difficult to obtain with spiramycin [5]; clinical use of this drug was never considered seriously in view of the fact that the inhibitory range for the majority of strains was 5μg. to 20μg. per milliliter. Vancomycin was not tested against a sufficient number of cultures to allow comparison of its activity with the other antimicrobials, and we have not had enough clinical experience with this drug to allow comment.

Evaluation of in Vitro Sensitivity Tests with Reference to Clinically Attainable Blood Levels.—For sensitivity tests of this type to be useful they must be interpreted in terms of concentrations achievable in vivo. The available data on this subject, being dependent upon dose, route of administration, and assay method, vary widely. Table 3 is a

TABLE 3.—*Criteria Employed for Sensitivity to Various Antibiotics*

Agent	Level of Sensitivity/Ml.
Penicillin (low)	≤ 5 units
Penicillin (high)	≤ 50 units
Erythromycin	≤ 5μ
Tetracycline	≤ 5μg.
Chloramphenicol	≤ 10μg.
Bacitracin (low)	≤ 1 unit
Bacitracin (high)	≤ 10 units
Neomycin	≤ 5μg.
Oleandomycin	≤ 5μg.
Novobiocin (Cathomycin)	≤ 10μg.
Novobiocin (Albamycin)	≤ 10μg.
Spiramycin	≤ 1μg.

compilation of concentrations which seemed to us to approximate those attainable with doses ordinarily employed in clinical practice nearly enough to allow an evaluation in these terms.[6-12] Two levels were selected for penicillin: The first (5 units per milliliter) is easily attained by administering 1,200,000 to 2,400,000 units of aqueous procaine penicillin daily. The second, although still within the therapeutic range, requires a dosage of 10,000,000 to 20,000,000 units daily in conjunction with probenecid.[13] Bacitracin was divided into two categories; only the lower concentration allows a safe blood level, but high concentrations can be reached in vivo if necessary, and for local application large amounts are entirely feasible.

With use of these arbitrary criteria the results of the tests for each group were evaluated in terms of the predicted bacteriostatic and bactericidal activity (Fig. 4). Nearly 40% of staphylococci were inhibited by 5 units of penicillin per milliliter, and almost 60% of staphylococci in both groups were sensitive to 50 units per milliliter. Indeed, penicillin in the higher concentration was as effective a bacteriostatic agent as erythromycin and considerably more potent bactericidally. The impression that most staphylococci are sensitive to chloramphenicol is borne out, but this drug had essentially no bactericidal effect. The striking sensitivity of 200 strains to novobiocin deserves emphasis. In the clinical group the only resistant strain was isolated from a child with empyema who had received novobiocin. The single carrier who harbored a novobiocin-resistant organism had not received the drug. In contrast, 25% of strains were resistant to oleandomycin in spite of the fact that this agent, alone or in combination, has not been used in The Johns Hopkins Hospital.

Considering only the agents commonly employed in staphylococcal infections, i. e., penicillin, erythromycin, tetracycline, chloramphenicol, oleandomycin, and novobiocin, and applying the criteria outlined in Table 3 as the basis for "sensitivity," it was noted that many strains were susceptible to several agents. This is illustrated in Table 4; 97% of organisms in the clinical group were inhibited by two, and 90%, by three agents. Similar results were observed in the carrier group. In striking contrast, 66% of strains

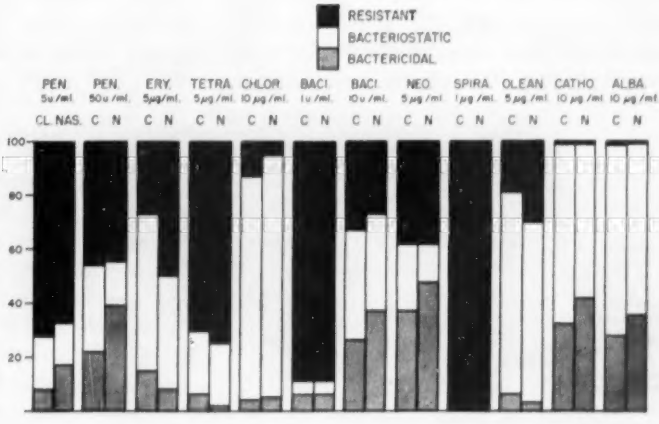

Fig. 4.—The sensitivity of 200 strains of staphylococci to 10 antibiotics, expressed in terms of attainable blood levels.

TABLE 4.—*The Sensitivity of 200 Strains of Staphylococcus to Multiple Antimicrobials*

		Agents, No.						
		6	5	4	3	2	1	0
		Strains, No.						
Clinical infections	Bacteriostatic	19	20	34	17	7	3	0
	Bactericidal	1	2	4	3	5	19	66
Carriers	Bacteriostatic	21	14	23	23	19	0	0
	Bactericidal	0	1	1	3	14	28	53

in the clinical group and 53% of the carrier strains were not killed by any agent in therapeutic concentrations.

Drug of Choice.—The results of the tests were further analyzed to determine which antibiotic inhibited each strain in the lowest concentration, and this agent was then designated as the "drug of choice." Whenever an organism was sensitive to 5 units of penicillin this was taken as the preferable drug. Penicillin was the "drug of choice" for 30% of the strains; novobiocin was the most effective agent against 43% and inhibited an additional 19% as effectively as other drugs; erythromycin was the most effective bacteriostatic agent for only 6% It is noteworthy that no effective bactericidal action was observed against 40% of the strains tested; of the remaining 60%, half were killed most efficiently by penicillin.

Bacteriophage Type.—Table 6 details the bacteriophage types of the organisms tested. Thirty-three coagulase-positive strains from clinical infections were available for typing. No strains were found in Groups I and II. Eleven were typical Group III types; 16 more fell into two predominant patterns (52/42B/44A/81 and 52/42B/81). Six strains were unaffected by the bacteriophages used. Strains lysed by Type 81 bacteriophage were almost uniformly resistant to penicillin in high concentrations.

Sixty-seven of one hundred organisms in the carrier group were typed. Of the 58 typable strains, 40 were of Group III and 15 were lysed in the pattern 52/42B/44A/81.

TABLE 5.—*Drug of Choice on the Basis of in Vitro Sensitivity Tests*

Drug of Choice	Infections		Carriers	
	Bacteriostatic	Bactericidal	Bacteriostatic	Bactericidal
Penicillin	28	22	32	37
Erythromycin	11	8	2	4
Novobiocin	36	21	50	22
Erythromycin or novobiocin	19		15	1
Erythromycin or novobiocin or chloramphenicol	3	1	1	
Oleandomycin	0			
Oleandomycin or novobiocin or erythromycin	2			
Oleandomycin or chloramphenicol	1			
Tetracycline		5		
None		43		36

TABLE 6.—*Relationship of Bacteriophage Type to Antibiotic Sensitivity*

Clinical Cases	No. Strains	Sensitive Strains, No.				
		Pen.		Ery.	Tet.	Chl.
		High	Low			
Groups I & II	0					
Group III	11	4	3	5	2	9
52/42B/81 (44A)	16	2	0	12	1	13
Not typable	6	3	2	4	3	4
Carriers						
Group I	3	3	3	3	3	3
Group II	0					
Group III (total)	40	24	13	15	7	39
Types 7 or 77 of Group III	17	17	11	9	3	17
52/42B/81 (44A)	15	0	0	13	0	15
Not typable	9	6	4	5	3	7

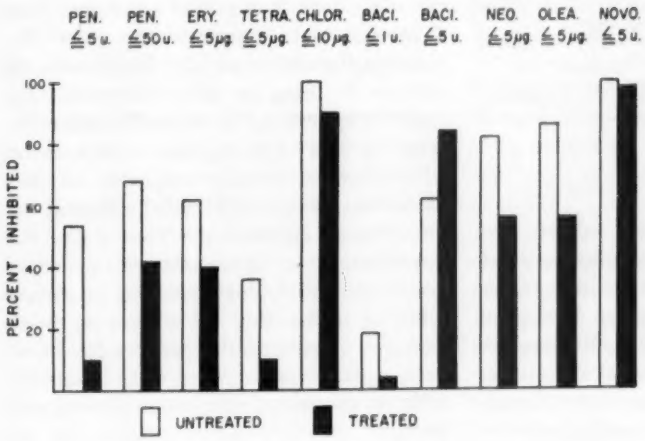

Fig. 5.—A comparison of the sensitivity of 50 strains of staphylococci from untreated carriers and 50 from patients who were receiving chemotherapy. Note the increase in resistant organisms in the treated group.

As has been pointed out by others,[14] resistance to penicillin was high among organisms belonging to Group III; penicillin-sensitive strains tended to lyse with Type 7 or Type 77 bacteriophage. The three strains from the carrier group that belonged to Group I were uniformly sensitive to all antibiotics. For any individual organism there was no predictable relationship between sensitivity, type, and previous exposure to certain antibiotics. Over all, however, the incidence of resistance to one or several antibiotics was far higher among strains obtained from patients receiving or recently treated with antimicrobials. As is shown in Figure 5, organisms from antibiotic-treated patients were significantly less sensitive to penicillin, erythromycin, tetracycline, neomycin, and oleandomycin than organisms from untreated patients. There was no appreciable difference in sensitivity to chloramphenicol and novobiocin in the treated and untreated groups. In vitro resistance bore no relationship to the antibiotic that patients had received. Most had received penicillin, and there was some increase in resistance to this drug; but the organisms were resistant to several other drugs which had not been employed in therapy. For example, twice as many strains were resistant to oleandomycin in the treated group despite the fact that this antibiotic had not been used.

Clinical Significance of in Vitro Sensitivities.—An attempt was made to correlate the outcome of therapy with the results of antibiotic sensitivity tests in the clinical group. The diagnosis of the patients from whom these organisms were isolated are listed in Table 7. The high incidence of blood-stream invasion emphasizes the fact that these were severe infections. The outcome of therapy is shown in Table 8. Complete information was available in 74 cases; 3 patients died before receiving antibiotics, 7 did not receive systemic chemotherapy and were successfully treated with surgery and with antibiotics locally, and in 16 cases data were insufficient to permit comment on the effect of chemotherapy. Thirty-three patients im-

TABLE 7.—*Diagnosis and Source of Organism in One Hundred Staphylococcal Infections*

Diagnosis	Source	Strains No.
Endocarditis	Blood	9
Bacteremia	Blood	
Purulent focus		17
Focus unknown		4
Furunculosis, cellulitis, wounds	Skin	24
Empyema	Pleural fluid	8
Lung abscess, pneumonia	Sputum	8
Cystitis or pyelonephritis	Urine	5
Enteritis	Stool	5
Osteomyelitis	Pus	5
Meningitis	Spinal fluid	1
Miscellaneous abscesses	Pus	
Ear or mastoid		4
Breast		2
Psoas		3
Pericardial cavity		1
Parotid		1
Pharynx		2
Nasolacrimal duct		1
Total		100

TABLE 8.—*Correlation of Outcome of Infections with in Vitro Sensitivities*

Outcome of Infection	Organisms, No.	
	Sensitive	Resistant
Improved on antibiotics alone	31	2
Improved with surgery and antibiotics	30	2
No improvement	8	1

proved with antibiotics alone; all but two of these harbored antibiotic-sensitive organisms. Thirty-two required surgical treatment in addition to chemotherapy. Several of these had been treated with antimicrobials but improved only after surgical drainage was instituted. Two strains of antibiotic-resistant staphylococci were eradicated after appropriate surgical treatment. In general there was excellent agreement between the results of in vitro tests and the response to therapy. The important place of surgery in the treatment of staphylococcal disease is well documented; the data presented here support this strongly.

Comment

The pattern of sensitivity to antibiotics of staphylococci tested in this laboratory has remained uniform for 18 months. One-third of strains were inhibited by 5 units per milliliter of penicillin, and 50%, by 50 units per milliliter. Furthermore, penicillin was bactericidal more frequently than any agent but bacitracin and neomycin. Although erythromycin remains effective against 65% of staphylococci, its killing effect is slight. Furthermore, there is little question from this and other reports [15,16] that refractoriness to erythromycin is increasing. Tetracycline is effective against only 25% of strains in concentrations which are practical clinically; the authors do not employ this drug routinely in staphylococcal infections. Chloramphenicol remains effective as an inhibitor of bacterial growth, but its bactericidal effect is insignificant. There is no indication whatever that oleandomycin offers any advantage over other agents, and, by the criteria used in this study, it would rarely, if ever, be designated as the "drug of choice." Its extremely poor bactericidal action has been mentioned and is perhaps the most discouraging evidence of all. Novobiocin, in addition to being an efficient bacteriostatic agent, is bactericidal in attainable concentrations for 25% of staphylococci. It is useful when instilled locally; empyema in five babies was successfully treated with oral and intrapleural novobiocin. The ability of staphylococci to circumvent the action of novobiocin and the high incidence of allergic reactions to the drug are, of course, disadvantages of considerable magnitude. However, it has already proved to be a valuable addition to the antistaphylococcal armamentarium.

The information gathered from these studies has led us to adopt a plan of therapy for staphylococcal infections which can be varied for the individual patient. In serious systemic infection, penicillin in a dosage of 20,000,000 to 40,000,000 units daily with probenecid is given. A second bacteriostatic agent, preferably erythromycin or chloramphenicol, is added in a dosage of 2 to 4 gm. daily. Early and adequate surgery is carried out whenever indicated. Even if sensitivity tests indicate resistance to penicillin, its administration is continued for at least a week, and it is discontinued only when there is clear evidence of no response. On the basis of in vitro tests the bacteriostatic drug can be changed to tetracycline, but it is our practice to withhold novobiocin, bacitracin, and neomycin if other agents can be used. The policy of holding novobiocin in reserve and restricting its use to those situations which cannot be managed in any other way has thus far prevented the appearance of a significant number of resistant strains in the environment.

The practice of using more than a single drug in the treatment of staphylococcal disease is an empirical one. That two drugs are better than one is an assumption, and it cannot be denied that antagonism is a distinct possibility.[17] However, the lack of certainty about the proper agent in any case when first seen justifies this procedure, and

until definitive evidence is presented to indicate that combined therapy is detrimental in patients with staphylococcal infection, it seems the proper course.

Bacitracin was used in only two patients in this series, although others have advocated its routine employment for staphylococcal sepsis.[18] We have seen no significant difficulty from bacitracin in a dosage of 80,000 to 100,000 units daily and would not hesitate to give it to any patient in whom penicillin was ineffective. It is a valuable drug for staphylococcal disease.

The importance of administering large amounts of penicillin, in spite of the fact that the organism may be relatively resistant in vitro, cannot be emphasized too strongly. Melton and Logue, employing such a regimen,[19] have reported cure in six of seven patients with staphylococcal endocarditis, and sterilization of the blood stream was also achieved in seven of nine patients in the present series who had involvement of the heart valves.

The regimen presented here is not a panacea for staphylococcal infection. The mortality rate in the entire clinical group was 5%; it was 16% among the patients with bacteremia. It is our opinion that with the use of antibiotics currently available an approach guided by in vitro tests, the patients' response, and a willingness to adapt treatment to the individual case offers the greatest hope in staphylococcal disease at present. Certainly this is preferable to reliance on new and untried (but highly publicized) drugs or fixed combinations of antibiotics now being marketed.[20]

Summary

The sensitivity of 200 strains of pathogenic staphylococci, including 100 from severe clinical infections and 100 from hospitalized nasal carriers, to penicillin, erythromycin, tetracycline, chloramphenicol, neomycin, bacitracin, oleandomycin, novobiocin, spiramycin, and vancomycin is reported. The bacteriostatic and bactericidal activity of these drugs were determined. It was found that penicillin continues to be a potent bacteriostatic and bactericidal agent in over 50% of staphylococcal infections. Resistance to erythromycin appears to be increasing, but the organisms were uniformly sensitive to novobiocin.

Resistance to one or several drugs did not correlate well with bacteriophage type or previous treatment with a single antibiotic. The outcome of the clinical infections was compared with these in vitro tests, and, in general, there was close agreement between the results obtained in the clinic and the laboratory. Finally, a suggested program for treatment of staphylococcal infections is outlined, emphasizing the importance of sensitivity testing, bactericidal action, and surgical drainage.

Mary C. Rose and Patricia Kammerer provided technical assistance.

The Johns Hopkins Hospital (5).

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Uropepsin Excretion

Studies in Three Hundred Patients

SOLOMON J. ROSENBERG, M.D., Louisville

The presence of a pepsin-like entity in the urine has been known for almost a century; Brücke [1] first mentioned it in 1861, Frouin [2] described it in 1904, and Gottlieb [3] further added to its understanding in 1924. It remained dormant until 1946, when Farnsworth [4] published a review of the literature, with comments on the absence of this pepsin-like substance in the urine of pernicious-anemia patients. The following year, Bucher [5] evaluated the effects of varied diets on this urinary substance, now termed "uropepsin," hereafter referred to as U-P (the end-product of uropepsinogen activation). The last decade has seen a renewed interest in U-P studies, further intensified by the impact of Selye's "Adaptation Syndrome" and the emergence of endocrinology from its early theoretical stage to the maturity of the corticotropin-cortisone era, and strengthened by innumerable practitioners who would spare their patients the discomforts of the stomach tube.

Our purpose in this paper is (1) to present our experiences in the study of U-P excretion while covering a kaleidoscope of diseases and derangements, (2) to compare these studies with the results of the many other workers in this fruitful vineyard, and (3) to assess the role of this laboratory test in clinical medicine.

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From the Medical Service and Medical Research Laboratory, Veterans' Administration Hospital, and the University of Louisville School of Medicine; Assistant to the Chief of the Medical Service, Veterans' Administration Hospital, and Assistant Professor of Medicine, University of Louisville School of Medicine.

Review of the Literature

West [8] noted the day-to-day constancy of U-P excretion; this is contradicted by the antithetical findings of Goodman.[9] Broh-Kahn [7] notes close agreement of the day versus night excretion, but West [8] finds a slight decrease in excretion in the afternoon and evening. Broh-Kahn [7] found no significant changes in U-P excretion due to volume, specific gravity, or acidity of the urine. A high-protein diet caused an increased U-P excretion in Bucher's study,[5] but Goodman [9] found a high-protein diet productive of normal values only. Bucher [5] also noted a decreased excretion by subjects given a high-carbohydrate diet. Several observers [5,7] found constant excretion patterns in subjects given normal diets.

Bridgwater et al.[38] found U-P excretion by males to be 60% greater than by females; decreased excretion was observed in pre-adolescents and "adults over 60." U-P and 17-ketosteroid excretion patterns correlated well in young men, according to Garst,[10] but rather poorly in older men.

Merten [6] found decreased excretion in infectious diseases and undernutrition; Tobler [13] noted significant elevations in patients after vaginal or abdominal surgery.

Both atropine [12] and propantheline (Pro-Banthine) [14] may cause a decrease in U-P excretion; the Rauwolfia drugs [41] exert little influence.

Numerous observers [9,11,12,15-19] have found significant increases in U-P excretion in cases of duodenal ulcer. However, some [9] have remarked on the significant percentage of patients with duodenal ulcer who excrete normal amounts of U-P. Others [12] report

less pronounced increases in excretion in patients treated with anticholinergic drugs.

While many [15-19] have emphasized increased U-P excretion by patients with gastric ulcer, others [9,11,12,21] have found excretion patterns well within the normal range.

Although normal U-P values [9,11,19] are common in gastric carcinoma, some observers [12,16,17,21] found a pronounced decrease in excretion. One study [18] reported an actual increase in U-P excretion.

Partial gastrectomy affects a decrease in U-P excretion.[6,11,12,16,17,26,27] Total absence of U-P excretion [9,11,16,18] occurs after total gastrectomy, confirming the studies of Mirsky et al.[22] in gastrectomized dogs and cats and supplemented by Hirschowitz' [23] work demonstrating the disappearance of plasma pepsinogen from the blood immediately after gastrectomy. No alteration in U-P excretions by the totally gastrectomized person occurs after corticotropin administration,[24] whereas increase in excretion by the person with partial gastrectomy does occur with corticotropin.[17,25] Vagotomy alone apparently produces little change in U-P excretion.[11, 26,27]

Near unanimity prevails [4,16,17,35] as to the marked decrease in U-P excretion by patients with pernicious anemia; many observers [9,11,15,18,22] report a complete absence of U-P in the urine of pernicious-anemia patients. A complementary study by Janowitz [34] shows a total absence of pepsin in the gastric aspirates of pernicious-anemia patients. Corticotropin does not produce or enhance U-P excretion in the pernicious-anemia patient.

Pronounced increases in U-P excretion occur on corticotropin administration.[8,11,12, 24,30] Similar increases have been reported with cortisone,[11] but this has not been uniformly noted.[39] Wolfson [36] found no change on giving corticosterone; Balfour [40] noted elevated excretion with testosterone. Gray et al.[25] found no significant changes on administering desoxycorticosterone (Doca), testicular hormones, adrenal androgenic hormones, and various pituitary hormones (growth, thyrotropic, gonadotropic).

Patients with Addison's disease, hypopituitarism, adrenogenital syndrome, or myxedema usually show decreased U-P excretion. Conversely, U-P excretion is unusually high in Cushing's syndrome and hyperthyroidism.[28,37]

Podore et al.[32] pointed out the "fortuitous" parallelism between gastric hyperacidity and increased U-P excretion, but this is negated by Rigler.[20] Others [30,31] have strongly questioned the validity of U-P excretion as a measure of gastric peptic or secretory activity, especially urging caution in using the U-P excretion as an index of adrenocortical activity without knowing the morphologic state of the gastric mucosa.[12,30] Many [28,29] have been disturbed by the development of active duodenal ulcers in patients on corticotropin-cortisone therapy; some [21,28] have emphasized the role of "stress." Gray [28] predicates an ancillary role for the steroid hormones in the hypothalamic-pituitary-adrenal-gastric axis, uropepsin being the end-product of this humoral mechanism. Hirschowitz [33] assails this concept, giving a varying renal clearance of pepsinogen and a varying plasma pepsinogen the stellar roles in the U-P drama.

Material and Method

The U-P determination was performed in 300 hospitalized veterans; the cases came from the entire hospital population, including samples submitted by the surgical and neuropsychiatric services. No restriction was placed upon the patient prior to or during the collection of samples, so that the patients differed in terms of activity, medication, and ongoing laboratory procedures. The majority of the group submitted three samples of urine, each being collected over a two-hour period; a small number represent a pooled six-hour sample. Collections were usually made between 8 a. m. and 2 p. m. Urine was collected in a bottle provided by the Medical Research Laboratory, containing 0.5 ml. of 25% sulfuric acid.

The determination was performed the very day of collection of samples; the method described by West, Ellis, and Scott [9] was followed. Results are expressed in terms of U-P units per hour, 1 unit being defined as the number of milliliters of acti-

vated urine ×10 required to give the end-point in 100 seconds. The control group consisted of 20 persons from the hospital staff, none of whom showed any evidence of disease on careful evaluation. The mean excretion in this control group was 30 U-P units per hour, with a standard deviation of 8.72; the normal range for our control group was 13 to 47 U-P units per hour. It should be noted that these mean values are those of our own laboratory; however, they do compare favorably with the 15 to 40 range described by West et al.[8]

Results and Comment

The U-P excretion was significantly elevated in cases of duodenal ulcer. Half of the group showed this elevation, whereas only 2 of the 87 cases fell below the normal. Normal values were obtained in slightly less than half of these cases. Similar results were obtained in the gastric ulcer group, although the dispersion of values was not as great. Surprisingly, the group of psychophysiologic gastrointestinal disease (patients with no objective evidence of organic disease of the stomach or duodenum despite a long-standing symptomatology) closely approximated these two ulcer groups, showing nearly equal distribution of values between the normal and the elevated. The absence of any significant difference between the latter group and the groups with organic ulcer renders the test worthless as a means of differentiating these entities. The question may be asked: "How useful is this test in suggesting a gastric malignancy?" Over half of the cases of gastric neoplasm fell in the below-normal group; a third, in the normal group, and 1 of the 15 cases revealed an elevated excretion. The trend toward low values is evident here; certainly, high values were infrequent, and in addition the difference between this group and the benign-ulcer series was statistically significant. An overlap in values did exist, but not in the extreme high or low values. If the results are interpreted thoughtfully some cautious conclusions can be made, although it would be folly to rely upon this test alone.

Analysis of a group of 23 cases of "other gastrointestinal disease" showed no significant differences from the control group, 16 of the group falling within the normal. This group included cases of hiatus hernia; diverticulum of the esophagus, stomach, or colon, and bleeding hemorrhoids. This might indirectly suggest that intrinsic alterations in gastric secretory activities are required before they are reflected in the U-P excretion changes.

A group of 14 nongastric malignancies was tested and showed a high mean value,

Data on Studies of Uropepsin Excretion

Group	Total No. Cases	Uropepsin Excretion, Units/Hr.					
		Mean	S.D.	Range	0—12*	13—47*	48—584*
Control	20	30	8.72	13–47†	--	19 (95.0)	1 (5.0)
Duodenal ulcer	87	58	41.00	10–234	2 (2.3)	41 (47.1)	44 (50.6)
Gastric ulcer	15	55	35.00	13–129	--	8 (53.3)	7 (46.7)
Psych. gastrointestinal dis.	11	58	39.00	18–167	--	5 (45.4)	6 (54.6)
Gastric Ca.	9	14	14.84	0– 50	5 (55.6)	3 (33.3)	1 (11.1)
Other gastrointestinal dis.	23	28	17.40	6– 78	4 (17.4)	16 (69.6)	3 (13.0)
Nongastric Ca.	14	50	63.55	2–269	3 (21.4)	8 (57.2)	3 (21.4)
Cirrhosis	20	29	26.96	0– 86	8 (40.0)	8 (40.0)	4 (20.2)
Gastrointestinal bleeding	4	66	34.71	21–118	--	1 (25.0)	3 (75.0)
Gastritis	3	55	28.60	32– 95	--	2 (66.7)	1 (33.3)
Part. gastrect.	10	22	17.75	9– 58	4 (40.0)	4 (40.0)	2 (20.0)
Vagotomy	8	51	43.72	17–141	--	5 (62.5)	3 (37.5)
Other diseases	26	31	16.65	4– 72	4 (15.4)	17 (65.4)	5 (19.2)
Pernic. anemia	4	0	0.00	0	4 (100.0)	--	--
Other anemias	7	16	12.93	4– 43	3 (42.9)	4 (57.4)	--
Posterolat. degen.	5	20	15.09	3– 44	2 (40.0)	3 (60.0)	--
Pulm. TBC	32	42	24.83	10– 96	1 (3.1)	22 (68.8)	9 (28.1)
Hepatitis	2	70	--	55– 86	--	--	2 (100.0)
Acetylsalicylic acid	4	62	51.20	3–144	1 (25.0)	1 (25.0)	2 (50.0)
Steroids	5	107	47.98	32–169	--	1 (20.0)	4 (80.0)
Hypopituitarism	1	6	--	6	1 (100.0)	--	--
Addison's dis.	1	19	--	19	--	1 (100.0)	--
Myxedema	4	48	33.53	13– 82	--	2 (50.0)	2 (50.0)
Hyperpituitarism	1	584	--	584	--	--	1 (100.0)
Cushing's syndrome	2	158	--	129–187	--	--	2 (100.0)
Hyperthyroidism	2	44	--	36– 52	--	1 (50.0)	1 (50.0)

* No. in parentheses indicates per cent.
† Obtained by calculating Mean ± 2 (S.D.), giving the 95% confidence level.

with 21.4% below and 21.4% above the normal values. The cause of this variation is purely speculative, although one might timidly postulate "stress" or metastases to the adrenal cortex in order to explain the altered U-P excretion.

Differentiating cirrhosis from benign ulcer has always been a knotty problem when one is faced with gastrointestinal hemorrhage and possible surgical intervention. A statistically significant difference was found between the group of 20 cirrhotics and the ulcer patients. Extremely low values tend to incriminate cirrhosis as a cause of the gastrointestinal bleeding, but again the overlap obtains in 60.2% of the group. A small group of four patients with bleeding from the gastrointestinal tract (etiology undetermined) showed no values below the normal, further enhancing the significance of low values as the salient feature in many bleeding cirrhotics. Even the three cases of "gastritis" (an x-ray diagnosis in which prominent gastric rugae are described) had values far removed from the subnormal excretion pattern of many patients with portal cirrhosis.

In contrast to the repeated emphasis in the literature on the extremely low values following gastrectomy, only 40% of the 10 patients who had undergone partial gastrectomy showed subnormal values. As near as could be determined these patients had received a "conservative" (approximately 60%) partial gastrectomy. The eight vagotomy patients came even closer to the control group, showing no values below the normal. Neither group was statistically different. Whatever alteration in gastric physiology is produced by these surgical procedures, the U-P excretion rate is not an accurate reflection of these changes.

A group of 26 cases with various diagnoses (congestive failure, hypertension, renal ailments, neuropsychiatric disorders, ventral abdominal hernia, arthritis, diabetes mellitus, bronchiectasis, and syphilis of the central nervous system) showed excretion figures that closely approximated the normal group. Other observers have often included cases of this type in their control groups; this study lends support to their assumption.

The four cases in the pernicious-anemia group consistently showed zero excretions, agreeing with the overwhelming consensus of other observers. Of further interest were the low values and the low range obtained in seven cases of other anemias; these values were statistically different from the normal group. Only three of these seven cases had a histamine achlorhydria, shedding very little light on the matter. A similar range was found in the five cases of posterolateral spinal degeneration, but the difference from the normal was not statistically significant. Neither of the two latter groups showed any values above the normal range. In view of the small number of cases in these groups the exact significance of these few observations cannot be evaluated.

Active pulmonary tuberculosis apparently affects the U-P excretion in a positive direction. Only 1 of the 32 cases under study showed a low U-P value, whereas 28% of the group proved to be above the normal range. Whether this represents a situation of "stress," acute or chronic, could be a subject of extensive dissertation; the difference was statistically significant regardless of the presumptive explanation. The two cases of hepatitis showed even higher values, suggesting perhaps a similar "stress" mechanism.

An attempt was made to assess the effect of drugs on U-P excretion. Sixty-one of the duodenal ulcer patients were receiving propantheline, atropine, or belladonna, whereas 26 patients in this group were not receiving such medications; there was no significant difference in U-P excretion between these subgroups. Two of the four cases receiving acetylsalicylic acid excreted more than normal, but the statistical difference from the normal group was only minimally significant. Four of the five patients being treated with prednisone or hydrocortisone showed excretion rates mark-

edly higher than the normal, the mean being 107.

The results in the small group of endocrinopathy cases studied were of interest but were too equivocal for valid comment. While the case of hypopituitarism showed low excretion, the patient with Addison's disease excreted normally; the four cases of myxedema showed U-P values not too far removed from the normal group. One patient with thyrotoxicosis excreted normally; the other showed only a mildly elevated excretion. The most striking and highest values noted occurred in the lone case of hyperpituitarism (irradiated pituitary tumor) where the preoperative value (584) rose to 843 during the immediate postoperative period (when replacement corticotropin therapy was instituted) and dropped slowly to 146, at which time methyltestosterone was the sole medication. Both patients with Cushing's syndrome showed significant elevations—129 and 187—which are consistent with the general agreement in the literature that the U-P excretion is somehow mediated by the pituitary-adrenal cortex pathway.

Summary and Conclusions

The uropepsin (U-P) excretions of 300 hospitalized veterans are described and evaluated. Comparison with the results and experiences with others is made; areas of agreement and contrast are delineated. A balanced appraisal of this relatively new laboratory modality suggests the following conclusions:

1. The U-P excretion values in most clinical entities overlap too frequently for ready incisive interpretation.

2. Modest usefulness is inherent in the procedure in differentiating (*a*) pernicious anemia from other anemias, (*b*) benign from malignant gastric ulcer when the U-P excretion is either extremely high or extremely low, and (*c*) the portal cirrhosis patients with gastrointestinal bleeding from the bleeding benign ulcer patients if the U-P value is extremely low.

3. The U-P excretion may not accurately reflect the physiologic changes produced in the human stomach by partial gastrectomy or vagotomy.

4. This laboratory determination acquires its greatest value at the present time when employed in endocrinology studies.

Dr. William P. Peak, formerly Resident in Medicine, and Dr. Edward Van Loon, formerly Chief of Research Laboratory, initiated this study, and Mrs. Mildred Edinger, M.T., provided technical assistance.

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Ardmore Disease

WILLIAM L. WILSON, M.D., Philadelphia; CHARLES D. WILLIAMS, M.D., Charlotte, N. C.; CAPT. SAUL L. SANDERS (MC), U. S. A. F., and R. P. WARNER, M.D., New York

This is a report of an outbreak and subsequent course of a highly infectious epidemic disease which occurred at Ardmore Air Force Base, Okla., in the fall of 1955. The disease is characterized by upper respiratory infection, prolonged malaise, generalized adenopathy, painful hepatosplenomegaly, and a pronounced tendency to relapse into a chronic smouldering illness of several months' duration. The clinical course superficially resembled that of infectious mononucleosis or infectious hepatitis, with some aspects reminiscent of epidemic pleurodynia. All of these diagnoses were considered originally but later rejected in view of the clinical course of over 100 patients.

The notable differentiating points were the absence of jaundice, consistently negative heterophil agglutinations, and the absence of atypical lymphocytes. We believe that this syndrome represents a clinical entity which, in sporadic form, may go unrecognized or be erroneously diagnosed as infectious mononucleosis or anicteric hepatitis. It is referred to as "Ardmore disease" since an etiological designation is not possible.

During the acute stage of the outbreak, throat washings were submitted to the 4th Army Laboratory at Fort Sam Houston, Texas. They were not successful in isolating any viral agents with use of embryonated eggs and suckling mice. At a later date throat washings and stool specimens from the hospital personnel at Sheppard Air Force Base, Texas, who contracted the disease, were sent to the U. S. P. H. S. Laboratory at Kansas City, Kan. They were also unable to isolate an etiological agent. In spite of the above failures, we still feel that the etiological agent is viral.

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Clinical Course

The disease may appear in sporadic or epidemic form. The first few cases were seen at Ardmore Air Force Base, Okla., in late August, 1955. In early September, 1955, the incidence increased rapidly to alarming proportions, with as many as 10 new cases daily. Initially some of the cases were treated as outpatients and sent home with marked restriction of activity; however, the seriousness of the disease was soon realized, and all patients were admitted to the hospital. Of those initially treated at home, most were later hospitalized. That facility soon became overcrowded, and it was apparent that other hospitalized patients as well as hospital personnel, including physicians, were rapidly contracting the disease. Subsequently, approximately 45 patients were transferred to the regional hospital at Sheppard Air Force Base, Texas, where most of the diagnostic studies herein reported were carried out. Despite rigid isolation technique and elaborate precautions, 2 physicians, 3 nurses, and 9 out of 15 medical corpsmen assigned to these patients at the Sheppard Air Force Base Hospital contracted the disease within two weeks. It was observed at that time that the incubation period appeared to be as short as 3 days and possibly as long as 10. The nature of the epidemic suggested that the infectious agent was probably airborne, associated with close contact. Several sporadic cases were also observed in newly arrived student airmen at Sheppard Air Force Base who had no known prior contact with the local epidemic.

The commonest complaint was of pain (77%), which many patients stated was in the lower chest and accentuated by deep

breathing or any jarring motion. The rest of the patients complained of pain in the upper abdomen which was accented by any jarring motion, such as walking. The pain of either type was often of a very severe nature, and some patients were initially noted to have rapid shallow respiration, since normal breathing was very painful. Others were noted to walk with short gingerly steps because of the jarring of their normal gait. The next commonest complaint was of a sore throat (66%), which in some cases was associated with rhinitis (29%). This symptom usually preceded the abdominal pain by a day or so and was usually described as being of a scratchy sensation. It was associated with only mild dysphagia and did not interfere with nutrition. Myalgia was also a very common complaint. Most of these patients complained of generalized muscular aching, but some complained of more localized pain, such as in the quadriceps or back. The severity of the pain was quite variable. Headache was also a common complaint, being present in 58% of the patients. It varied in intensity but was never severe and was usually described as being frontal in type. Nausea was described by 54% of the patients but was usually mild. Vomiting was unusual and severe in only two instances. In the other cases it only lasted a few days (Table 1).

TABLE 1.—*Symptoms*

Complaint	No. Pts.	%
Abdominal pain	49	77
Myalgia	43	68
Sore throat	42	66
Malaise	40	63
Headache	37	58
Nausea	34	54
Vomiting	13	20
Rhinitis	18	29
Other	47	75

Examination of the patients on admission usually revealed a young white male who appeared acutely ill. The more acutely ill patients would hold their arms crossed on their chest, so as to splint the upper abdomen and lower chest. The admission temperature was over 98.6 in 49% of the patients. Pharyngitis, which consisted of injection of the pharynx with lymphoid hyperplasia, was present in 75%.

Abdominal tenderness was present in 90% of the patients and in many was so marked that the patients would try to prevent the examiner from examining them. Thirty-eight patients had tenderness in both upper quadrants; seventeen, in the right upper quadrant only, and two, in the left upper quadrant. On admission 70% of the patients had palpable livers, which were difficult to feel because they were extremely soft in consistency and many of the patients were not too cooperative because of the pain caused by palpation. During the course of the illness, the livers of 92% of the patients became palpable. Spleens were palpable in 28% of the patients on admission and were acutely tender. The number of palpable spleens increased to 48% during the course of hospitalization. Tender lymphadenopathy was present in at least three general areas. The posterior cervical nodes were involved in 95% of the patients. The nodes were small, soft, and quite tender, often causing the patient to wince when they were palpated. Other less commonly found physical findings were muscle tenderness in approximately one-third of the patients and a discrete papular rash in three of the patients. It should be noted that neither pleural nor pericardial friction rubs was heard in any patient, even though these findings were carefully looked for (Table 2).

TABLE 2.—*Physical Findings*

Finding	No. Pts.	%
Lymphadenopathy	60	95
Abdominal tenderness	57	90
Both upper quadrants	38	
Right upper quadrant	17	
Left upper quadrant	2	
Pharyngitis	54	75
Palpable liver		
On admission	44	70
During hospitalization	58	92
Palpable spleen		
On admission	17	28
During hospitalization	30	48
Temperature on admission		
Over 98.6°F	31	49
Over 100°F	6	9
Highest temperature		
Over 98.6°F	63	100
Over 100°F	31	49

Laboratory Findings and Blood and Liver Tests

Although the clinical data have shown definite hepatitis, the laboratory data have certainly not been diagnostic of this disease. Hematological studies showed no anemia or thrombocytopenia. Fifteen patients had an initial WBC of over 10,000 — 10 showed a normal differential, 3 showed increased lymphocytes, and 2 showed increased neutrophils. Forty-eight patients had normal total white cell counts — 24 had a normal differential, and 24 had an increase in lymphocytes. Peripheral blood films were examined by several observers for atypical lymphocytes, which were so occasional as not to be even suggestive of infectious mononucleosis. Several patients (28%) were found to harbor β-hemolytic streptococci on routine throat culture. These were treated with a 10-day course of penicillin, although they showed no clinical evidence of streptococci sore throat. Heterophil agglutinations were consistently and repeatedly negative.* Agglutination studies for typhoid, paratyphoid, Brucella, Proteus OX19, Q-fever, and lymphogranuloma venereum were done on most of the patients and were negative.

Liver-function tests were done at frequent intervals. The commonest abnormality was an elevated cephalin-cholesterol flocculation, in which 86% had either a 2+ reaction at 24 hours or 3+ at 48 hours within 10 days. In 62% of the cases there was abnormal sulfobromophthalein (Bromsulphalein), retention of over 5% at 45 minutes (5.0 mg. of dye per kilogram of body weight). The serum bilirubin was elevated in only two instances and then to just 1.75 mg. per 100 cc. total. The thymol turbidity was rarely elevated and then only in questionable range. Reversal of the albumin-globulin ratio was noted in 11% of the cases. Determinations of alkaline phosphatase and urine urobilinogen were not abnormal (Table 3).

TABLE 3.—*Laboratory Findings*

Test	No. Pts.	%
Cephalin-cholesterol flocculation		
2+ at 24 hr. or 3+ at 48 hr.	54	86
Sulfobromophthalein		
Over 5% retention at 45 min.	39	62
White blood cell count over 10,000	15	24
Normal differential	10	
Increased lymphocytes	3	
Increased neutrophils	2	
White blood cell count 5000–10,000	48	76
Normal differential	24	38
Increased lymphocytes	24	38

Dr. John T. Galambos, of the U. S. P. H. S., Chamblee, Ga., did special studies on the serum from eight patients, including electrophoretic studies, determination of mucoprotein levels, and C-reactive protein determinations. Minimal and nonspecific increases in γ-globulin were found in five patients. The serum mucoprotein levels were elevated in all cases, ranging between 96 and 198 mg. per 100 cc. (normal, 55-85 mg. per 100 cc.). This is in contrast to infectious hepatitis, in which low values are usually found. The C-reactive protein studies showed no significant abnormalities.

Lymph-node biopsies were performed on 17 patients. Fourteen showed reactive hyperplasia; one, reticulum-cell hyperplasia, and two, no disease. Numerous special staining techniques failed to reveal any significant diagnostic features.

Liver Biopsy

Fourteen liver biopsies were done, and because of conflicting reports from several pathologists who reviewed the specimens one of the authors requested Dr. Hans Popper to review them. His report was that all specimens showed a "mild nonspecific hepatitis reaction." The findings consisted of mild Kupffer-cell mobilization, slight ductule proliferation, and widely dispersed scanty round-cell infiltration.

There was one complication after liver biopsy. This occurred in a 21-year-old patient who had normal coagulation studies prior to biopsy. The complication was most unusual in that the patient did well after the procedure and continued to do well until the night of the sixth post biopsy day. At this

*As a check on the procedure, heterophil agglutinations were repeated at three different laboratories and were consistently negative.

time he began complaining of right upper quadrant pain. At surgery there was found a funneled-out area at the site of biopsy, which was subcapsular, going over the dome of the liver and down to the anterior border. This entire area contained clotted blood. After surgery the patient had continued bleeding from the site for approximately two weeks. After the cessation of bleeding further surgery was required, as the patient had developed a sterile abscess in the indentation left by evacuation of the clotted blood. The patient survived the procedures and has done well.

During the initial hospitalization of the patients the course of the disease appeared benign and certainly gave us no indication of the difficulties to be encountered subsequently. The majority of the patients were hospitalized about four weeks on their first admission, being treated with bed rest and high-protein high-carbohydrate diet, with supplemental vitamins. After discharge they were given two weeks' convalescent leave. On return they were examined and laboratory tests were repeated. If examination failed to reveal evidence of hepatic dysfunction they were returned to limited duty for one month and then full duty.

A typical course for the initial admission would be as follows. The patient, who was quite fatigued, spent the first 24 to 48 hours sleeping and would get out of bed only to go to the bathroom. After this period of time he felt better, with loss of malaise and definite improvement of the abdominal pain. If the liver was not palpable on admission it was by the fourth day and, in some instances, was 7 to 10 cm. below the costal margin. At the end of the first week the patient no longer complained of lymph-node tenderness but still had hepatic and splenic tenderness, which was of a milder degree and bothered him only on walking, laughing, or sneezing. During the second week there was continued improvement regarding subjective complaints and the liver tenderness decreased markedly, being present on vigorous palpation only. During the third week the temperature returned to normal and usually stayed. The liver began decreasing in size during the third week, and by the end of the fourth week had usually regressed to the costal margin. The lymph nodes had undergone partial resolution by this time, even though they were still palpable. Splenomegaly, if present, disappeared more rapidly than did the hepatomegaly. Also it should be noted that splenomegaly on the initial admission was never marked and did not exceed 2 to 3.5 cm. below the left costal margin. At this time it was felt that this was a self-limited disease of viral etiology. It certainly resembled infectious hepatitis and infectious mononucleosis, but we feel that it is a separate and distinct clinical entity. The etiological agent apparently attained a high degree of infectivity and then waned, which is the only explanation we have for lack of further spread. We felt that we had followed a very conservative course of therapy as regards activity and certainly did not expect any further difficulty with the disease. This concept was quite wrong, and recurrences were far more severe and incapacitating than the original illness, as is noted by the breakdown of length of hospitalization (Table 4).

Report of Cases

CASE 1.—A 19-year-old white youth was first hospitalized at Sheppard Air Force Base on Oct. 20, 1955, with a history dating back two weeks prior to that time. The history consisted of head cold, left-upper-quadrant abdominal pain accentuated by coughing and deep breathing, and nausea and vomiting, which also accentuated the pain. Physical examination revealed a palpable tender liver and spleen and generalized tender lymphadenopathy. Positive laboratory findings consisted of a mild increase in lymphocytes and 3+ cephalin flocculation. He ran a low-grade fever for three weeks and then became afebrile. He was allowed to ambulate for a few days and remained asympto-

TABLE 4.—*Total Length of Hospitalization*

No. Days	No. Pts.	%
1–30	8	13
31–50	13	21
51–70	17	27
71–100	5	8
101–150	5	8
Over 150	15	24

matic. He was then given two weeks of convalescent leave. On his return he was still asymptomatic, and the physical examination was within normal limits. Therefore he was returned to duty. He did well until mid-December, 1955, when, during a Christmas leave at his home in Michigan, he experienced an episode of very sudden and severe left-upper-quadrant abdominal pain, lasting six to seven hours. On New Year's day he had a recurrence of this pain, except that on this occasion it was largely in the midline of the abdomen and of sufficient severity to force him to stop the car he was driving. He was taken to Selfridge Air Force Base Hospital, where he was admitted. The pain lasted two to three days; he was allowed to ambulate, and after one week he was discharged from the hospital. Upon his return to Sheppard during the second week of January, 1956, he did not feel well in general, complaining of fatigue, weakness, and recurrent twinges of pain in the upper abdominal region. He was seen in the dispensary and given a light-duty excuse. At that time he also noted a mild upper respiratory infection and complained of anorexia. In spite of this, he had gained from 143 to 159 lb. since his previous admission, in October, 1955. On Jan. 20, 1956, he was readmitted to the hospital. On this day he had sustained a minor trauma to the abdomen and, because of continued upper abdominal pain, was hospitalized.

Physical examination at this time revealed a temperature of 99.8 F; pulse, 80; blood pressure, 124/86. He appeared well developed, well nourished, and in no particular distress. Positive findings consisted of injection of the pharynx and marked lymphoid hyperplasia of the pharynx. The liver was down 1 to 2 fingerbreadths below the right costal margin and was moderately tender. The spleen tip was felt 1 fingerbreadth below the left costal margin and was quite tender. Slightly tender generalized lymphadenopathy was also present.

Laboratory Findings.—At the time of admission the hemoglobin was 14 gm. per 100 cc.; RBC was 4,750,000; platelets, 210,000; WBC, 8100, with a normal differential. The urinalysis was within normal limits. Prothrombin time was 100%; heterophil agglutination was negative; total serum bilirubin was 0.50 mg.; total protein was 6.6 gm. per 100 cc., with albumin 5.0 gm. and globulin 1.6 gm. Throat culture revealed α- and γ-streptococci, and repeated culture revealed α- and β-streptococci as well as hemolytic staphylococci. Serology was negative, and a stool culture revealed no significant pathogens. Sedimentation rate was 1.0 mm. on April 5, 1956, and WBC was 14,100, with a normal differential. On July 10, 1956, WBC was 15,450, with a normal differential. On July 13, 1956, WBC was 14,150, with a normal differential. On Aug. 14, 1956, WBC was 15,200. Serum bilirubin was normal on July 31, 1956. The chest x-ray was normal. Cephalin-cholesterol flocculation and sulfobromophthalein tests are shown in Table 5.

TABLE 5.—*Results of Cephalin-Cholesterol Flocculation and Sulfobromophthalein Tests*

Date	Ceph. Floc. (24 Hr.)	Sulfobromophthalein Retention (45 Min.), %
2/28/56		6.9
4/16/56	4+	
4/30/56		9.4
5/21/56		9.4
5/31/56	4+	
7/31/56	3+	6.5
8/7/56	3+	

Course in Hospital.—The evaluee initially was maintained with bed rest, nutritious diet, and vitamin supplements. The discovery that throat cultures revealed β-streptococci prompted a 10-day course of penicillin treatment. During the first month in the hospital, generalized lymphadenopathy persisted, as did anorexia, hepatosplenomegaly, epigastric pain and tenderness, sore throat, and occasional vomiting. Low-grade fever continued during the first three months in the hospital, and after this time his fever curve gradually returned to normal. Lymph nodes became less tender and swelling gradually, although never completely, subsided. The liver and spleen became larger, and at this time the liver extended 2 fingerbreadths below the right costal margin and was somewhat tender. A moderately tender spleen tip was felt extending 2½ fingerbreadths below the left costal margin. As of Aug. 17, 1956 (eight months after readmission), the patient was still symptomatic and was separated from the service.

CASE 2.—A 22-year-old white man was hospitalized at this installation on Oct. 18, 1955, and was discharged on Dec. 9, 1955, with the diagnosis of "Ardmore disease." At the time of that hospitalization his history was characterized by an upper respiratory infection, slight stiffness, nausea, vomiting, and pain in both upper quadrants. The physical examination on that occasion revealed enlarged and tender liver and generalized lymphadenopathy. Certain flocculation showed a value of 3+. Other laboratory studies were completely normal. He remained febrile for the first three and one-half weeks in the hospital. His fever gradually subsided, as did his liver enlargement. From the time of his discharge from the hospital until his hospitalization on Jan. 21, 1956, he noticed occasional twinges of right-upper-quadrant pain. About one week prior to this admission he had the onset of an ordinary head cold with rhinitis. On the day prior to this admission he noted the onset

of nausea, vomiting, and increased upper abdominal pain.

Physical Examination.—Physical examination at the time of admission showed a temperature of 98 F; pulse, 84; blood pressure, 122/80. Significant positive findings consisted of mild injection of the pharynx and slight reddening of the mucous membranes of the nose, with excessive mucus. The liver edge was soft and tender and extended 2 fingerbreadths below the right costal margin. The spleen tip was only slightly tender and could be felt below the left costal margin. Several pea-sized nontender lymph nodes were felt in both posterior and anterior cervical chains. Moderately enlarged nontender nodes were present in both axillary and inguinal regions.

Laboratory Findings.—At the time of admission, hemoglobin was 15 gm. per 100 cc.; sedimentation rate, 4 mm.; WBC, 7100, with 58% neutrophils, 16% lymphocytes, 10% monocytes, 12% eosinophils, and 4% bands. Cephalin flocculation was 1+; heterophil screen test, negative; total protein, 7.4 gm. per 100 cc., with 5.2 gm. albumin and 2.2 gm. globulin; thymol turbidity, 2.5 units; serum bilirubin (total), 0.75 mg. per 100 cc.; sulfobromophthalein test, 1.6% dye retention in 45 minutes; urinalysis, within normal limits. Numerous stool specimens were negative for ova, parasites, or significant amounts of occult blood. Prothrombin time was 89% of normal. Bleeding time, coagulation time, and platelet counts were normal. Chest x-ray was normal. Serology was negative. Currently complete peripheral blood cell counts are within normal limits, as is the urinalysis. Serology is negative, and all liver chemistries are within normal limits. Esophagram on June 3 was normal.

Course in the Hospital.—On admission the patient was maintained on a strict bed-rest regimen. During the first week his spleen enlarged further until it was palpable 1½ fingerbreadths below the left costal margin and was quite tender. Pre- and postauricular lymphadenopathy developed. Pharynx became markedly injected, and the evaluee noted marked lassitude and easy fatiguing, associated with the development of stiffness of the shoulders, back, and chest. During this period of time he also developed a low-grade fever. Bed rest was continued during the first month of hospitalization. He was then allowed some ambulation in spite of persistent lymphadenopathy and hepatosplenomegaly. He felt somewhat improved on ambulation. On March 28, 1956, a biopsy of a lymph node from the left axilla was performed, with a nonspecific reaction. During the next month and one-half, no change was noted in the hepatosplenomegaly, and the patient ran an intermittent fever which would last for several days. In addition to occasional episodes of vomiting and persistent upper quadrant pain, a weight loss of over 15 lb. ensued from the time of admission. At the end of April, 1956, the patient was allowed to leave the hospital. On return he felt fairly well. The liver had decreased in size, so that the edge extended only 1 fingerbreadth below the right costal margin. The spleen tip was barely palpable below the left costal margin. The patient was again given bed rest and, in spite of this, over the next two weeks the liver and spleen enlarged further and he continued to have right-and-left-upper-quadrant pain and tenderness. At that time, the sulfobromophthalein tests and all liver chemistries were normal. On June 22, 1956, transthoracic needle biopsy of the liver was performed, with a diagnosis of acute, nonspecific, liver degeneration.

During the following two weeks there was some improvement in symptoms, and the evaluee was allowed to ambulate. At this time (Aug. 9, 1956), the patient felt well except for occasional vague abdominal discomfort. The liver became rather firm and was felt 2 to 2½ fingerbreadths below the right costal margin. The spleen tip was nontender also and could be felt 2 fingerbreadths below the left costal margin. At this time the patient was discharged from the service, since it was felt that he was no longer capable of performing duty.

Comment

As to what the final prognosis is in these patients, we are still totally in the dark. It is a disease with several manifestations and apparently involves the reticuloendothelial system in a rather widespread manner. Probably the most serious aspect of the disease is the marked enlargement of the liver, yet the findings on biopsy or liver-function tests are certainly not what one would expect to have. The rather mild changes that were seen on liver biopsy are extremely difficult to correlate with the marked persistent enlargement of the liver seen in some of the patients. These changes, as well as those seen in the lymph nodes, are nonspecific reactions and can be seen in a wide variety of systemic diseases but are not indicative of intrinsic or primary liver disease. What the ultimate histological picture will be, unfortunately, is a matter of conjecture.

In spite of the many similarities to both infectious mononucleosis and infectious hepatitis, this disease certainly does not fit the diagnostic criteria for either. Infectious

mononucleosis, which some of the patients had had in the past, can definitely be ruled out because of the consistently negative heterophil agglutinations. Random serum specimens were sent to other laboratories as a check, and their results were also consistently negative. Also, none of the peripheral blood films were even suggestive of infectious mononucleosis [1]. The possibility of anicteric infectious hepatitis is ruled out, and usually this condition is seen in epidemics were the great majority of the patients do have jaundice.[2,3] Also, the clinical course, especially as regards the occurrence of associated upper respiratory involvement and the generalized tender adenopathy, is not the type picture that is seen in infectious hepatitis.

It is interesting to note the marked similarity of the 43 cases reported by Chauncey and Zatz [4] that occurred at Lowery Air Force Base, Colo. Their findings were quite similar to ours. Their range of hospitalization was from 18 to 155 days, which is not too different from that in the present report. However, they did not report relapses such as we have seen, nor did they report the degree of abnormalities in liver-function tests. This latter is noteworthy in that they reported abnormal liver-function tests in only 11 cases, whereas hepatic enlargement was present in 40 of the 43 cases. However, they did report that at the time of discharge from the hospital 18 of their cases still had enlarged livers and 4 had enlarged spleens. We wonder if such patients shouldn't have received either further hospitalization or separation from the service. In their report, upper respiratory involvement was present in almost all cases; however, liver enlargement was noted in less than half of the cases on admission, but it did become enlarged in 40 cases by the end of the second week. The temperature curves of their patients also initially showed a slight elevation, which subsided within a short period of time. One of the most important comparisons is that the patients of both series complained of marked abdominal pain, which was accentuated by respiration and aggravated also by early ambulation. Also, in reviewing the articles by Zimmerman and Thomas,[5] Denber and Liebowitz,[6] and Dominici,[7] which were all referred to an anicteric hepatitis or anicteric virus hepatis, there were numerous similarities. The cases reported by Zimmerman are more interesting because of the fact that all had enlarged livers and several ran a very chronic course, in which early ambulation brought a return of symptoms.

Summary and Conclusions

Presented is a series of 63 cases of what we refer to as Ardmore disease. It is a disease characterized primarily by the occurrence of an upper respiratory infection, marked tender hepatomegaly, tender lymphadenopathy, and low-grade fever. It is probably due to a virus. The most remarkable feature of the disease is the fact that in spite of marked hepatomegaly there is not the derangement of liver function that one expects, nor is the histological picture what one expects. Also, the number of relapses is certainly unusual for what appeared to be a very benign disease, and the relapses are of a much severer and more chronic nature than the original disease process.

We feel that this is a definite and distinct clinical entity in spite of the fact that at the present time there is not a specific diagnostic test available. However, we do not feel that it is a new disease but rather one that has been seen and mistaken for infectious mononucleosis and anicteric infectious hepatitis. It is probably the same disease that is reported in References 4 to 7.

Dr. Hans Popper reviewed all of the liver biopsy specimens.

This study was carried out while Drs. Wilson, Williams, and Warner were stationed at the U. S. A. F. Hospital, Sheppard Air Force Base, and Dr. Sanders was stationed at the U. S. A. F. Hospital, Ardmore Air Force Base.

The Hahnemann Medical College and Hospital of Philadelphia, 230 N. Broad St. (2).

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The Use of Radioactive Fat in the Study of Absorption in Various Disease States

DONALD BERKOWITZ, M.D., and DAVID SKLAROFF, M.D., Philadelphia

Until recently, methods to detect abnormalities in fat absorption have been based on procedures that are difficult to obtain and technically difficult to perform in the average hospital, i. e. fecal fat studies, chylomicron counts, vitamin A tolerance tests, and plasma lipid determinations. A measure of pancreatic enzymes by intubation techniques is likewise not generally available.

The accessability of I^{131}-labeled triolein now makes it possible to study fat absorption much more readily. Since Thannhauser and Stanley first reported their results, in 1949,[1] a large experience has accumulated which attests to the simplicity and reliability of the method.

We have attempted to evaluate the radioactive fat (RAF) test in a large general hospital, where, because of laboratory limitations, the assessment of fat malabsorption has always been difficult. The present study reviews our findings with 200 such tests.

Procedure

In general, we have followed the procedure outlined by Ruffin.[2] Two emulsions, a "hot" and a "cold," are prepared. Each contains equal quantities of peanut oil and water plus a few milliliters of Tween 80. In addition, 5 ml. of I^{131}-labeled glycerin trioleate are added to the hot mixture.

Thyroid uptake of I^{131} is prevented by administering 10 drops of strong iodine (Lugol's) solution three times on the day before the test.

After a 12-hour fast each patient is given a test meal which consists of that volume of "hot" emulsion containing 50 μc. of I^{131} plus additional "cold" emulsion to make a final total quantity of 1 ml. per kilogram of body weight. In some cases 20 gm. of barium sulfate was also added to the test meal, which made it possible to follow gastric emptying by serial fluoroscopic examinations.

After the patient drinks the test meal the container is rinsed out several times with warm water, and these washings are also ingested. Several additional washings are then made and are assayed for residual radioactivity. This is taken into account in calculating the total activity actually administered.

Venous blood samples are then taken until a peak radioactivity level has been reached. Each sample is counted in a scintillation well counter. With the given activity in a 2 ml. aliquot and the calculated total blood volume (based on a factor of 7.2% of the body weight), the total blood radioactivity can be determined and expressed as a percentage of the original ingested material. The total amount of urine excreted during the next 24 hours is also collected and its radioactivity also measured.

Results

1. *Normals.*—Figure 1 shows average percentage of ingested radioactive triolein in the blood at various time intervals in a group of 25 normal controls. The shaded area represents plus or minus one standard deviation. The peak blood level occurred most frequently between the fifth and sixth hours and was approximately 16% of the dose of fat given.

2. *Sprue and Pancreatic Disease* (Fig. 2).

Five patients with sprue were studied. All had marked steatorrhea, and the blood isotope curve was flat in each case. Ten patients with chronic pancreatitis confirmed by operation have shown significantly lower-than-normal blood isotope levels. All of these patients had some degree of steatorrhea. In a group of cases with a history of a

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From the Departments of Medicine and Radiology, Albert Einstein Medical Center, Northern Division.

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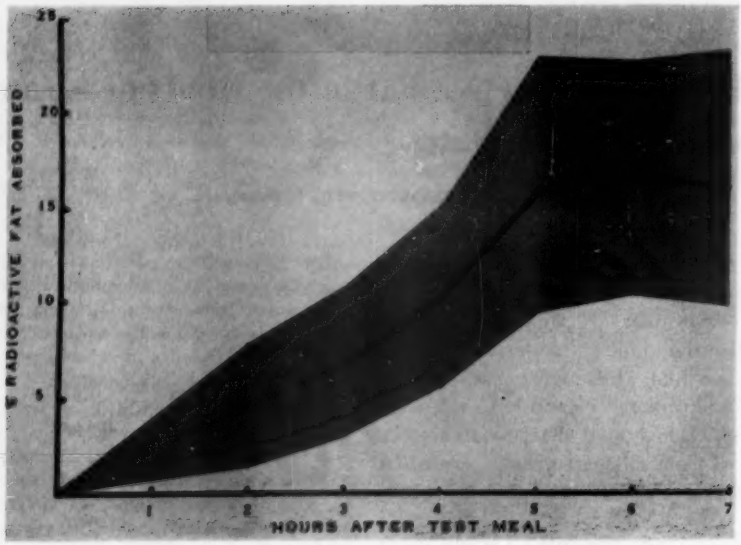


Fig. 1.—I^{131}-labeled blood fat levels (average curves) in normal controls. Shaded areas represent plus or minus one standard deviation.

previous episode of acute pancreatitis who did not have steatorrhea, blood values were within normal limits.

3. *Other Gastrointestianl Diseases* (Fig. 3).—Ten patients with duodenal ulcers and ten patients with irritable-bowel syndrome have been studied. Results in all did not differ significantly from the normals.

4. *Subtotal Gastrectomy State* (Fig. 4). We have been able to perform the test on 15 subjects who had subtotal gastrectomy. In each case at least three months had elapsed since the operation. Treated as a group, the averge blood levels were not significantly lower than normal. Six of the fifteen (40%), however, did have abnormally low values. Shingleton [3] has studied a much larger group of patients after gastric surgery with the RAF technique and found the average blood levels to be lower than normal. Forty-five per cent of his subjects had abnormal values.

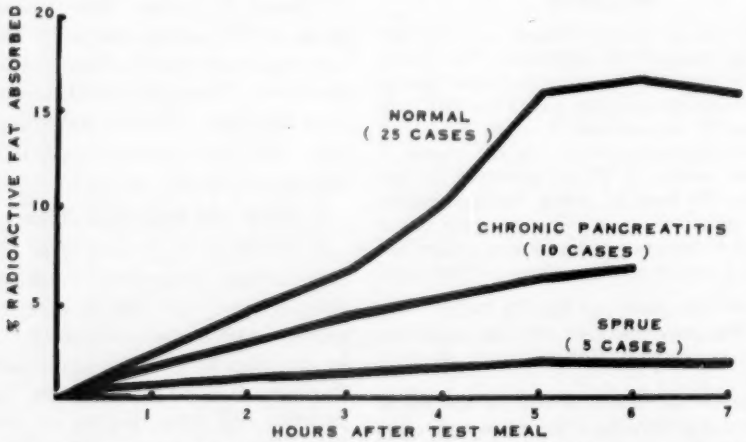


Fig. 2.—I^{131} triolein absorption in sprue and chronic pancreatitis (average curves).

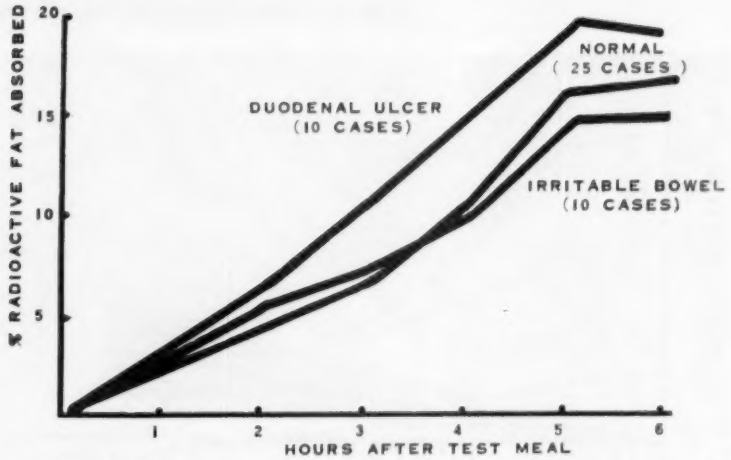


Fig. 3.—I^{131} triolein absorption in duodenal ulcer and irritable-bowel syndrome (average curves).

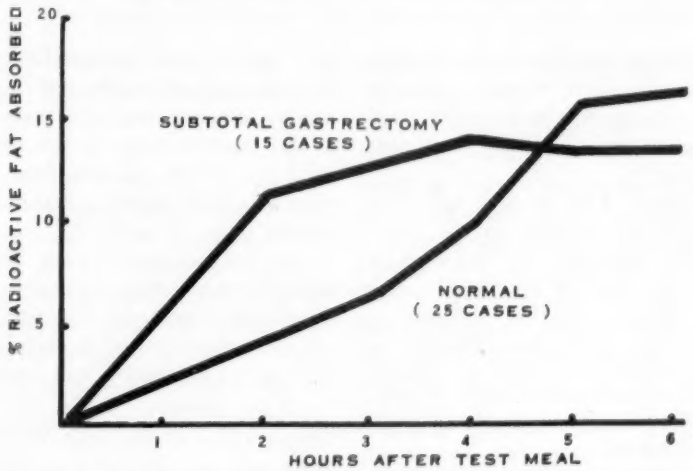


Fig. 4.—I^{131} triolein absorption in patients after subtotal gastrectomy (average curves).

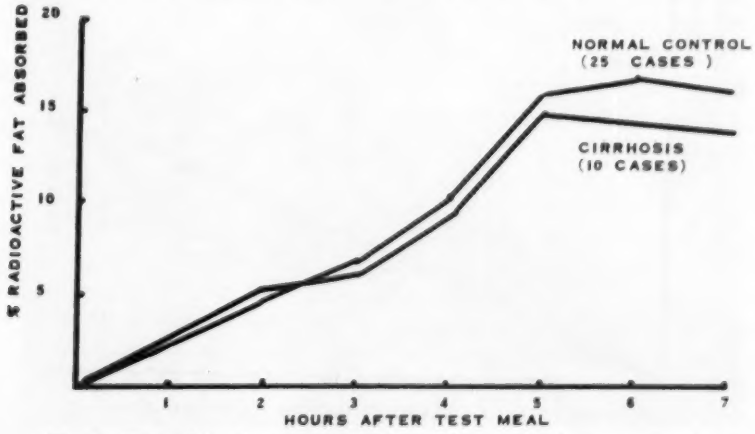


Fig. 5.—I^{131} triolein absorption in patients with cirrhosis (average curves).

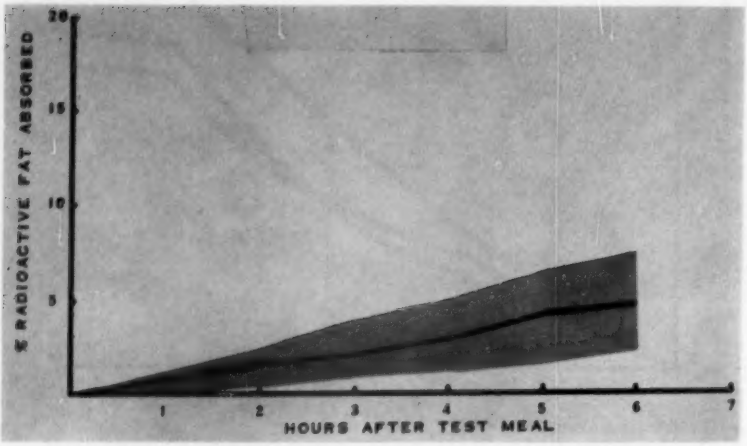


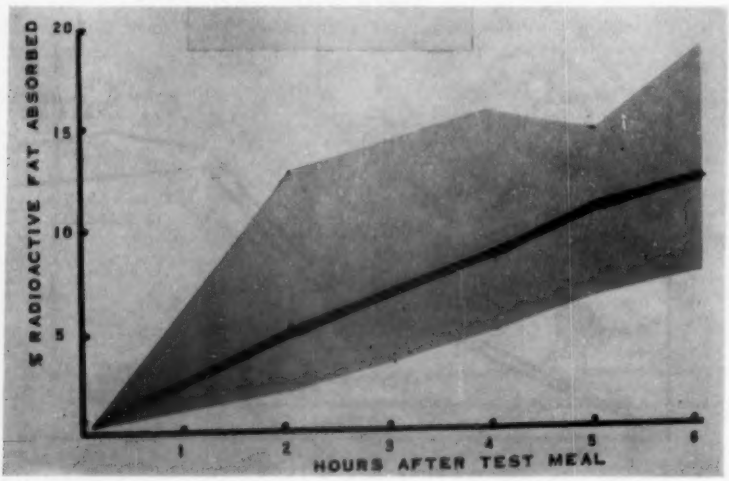
Fig. 6.—I^{131} triolein absorption in extrahepatic obstruction (average curve with range of individual values).

5. *Liver Disease and Jaundice.*—We have performed a radioactive triolein test on 10 patients with cirrhosis who were not jaundiced. In each case a normal result was obtained (Fig. 5).

Twenty patients with jaundice have been studied. In 10 the etiology was an extrahepatic block confirmed by operation or autopsy. In the other 10 the clinical course plus liver biopsy material indicated a parenchymal type of jaundice. The absorptive patterns in these two types of jaundice have been rather characteristic. In those with extrahepatic jaundice the average blood isotope level was markedly depressed, with a very narrow range in the entire group (Fig. 6). In the nonobstructed group this value was much higher, although lower than normal (Figs. 7 and 8).

This test has been of great value to us in several cases where the etiology of the jaundice was in doubt. One was a 46-year-old white man with an inconclusive history, a negative examination, and equivocal liver-

Fig. 7.—I^{131} triolein absorption in nonobstructive jaundice (average curve plus range of individual values).



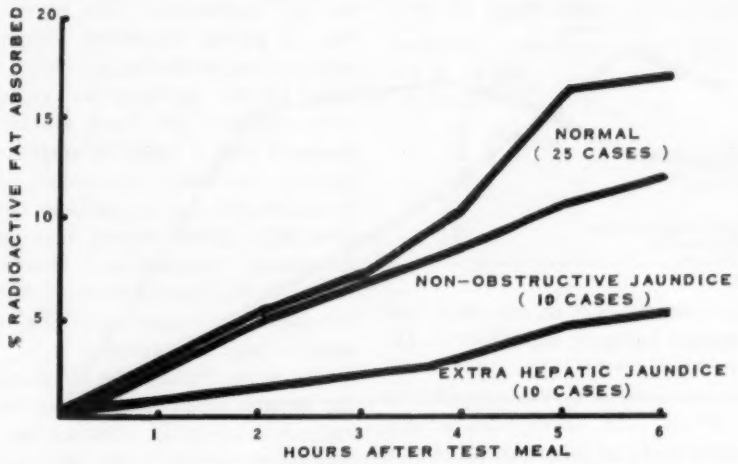


Fig. 8.—I^{131} triolein absorption in obstructive and nonobstructive jaundice (average curves).

function tests. On the basis of two fat studies which indicated obstruction the patient was explored, and a common-duct stone was found.

Another case was that of 53-year-old white woman who gave a typical history and had liver-function tests that corroborated the clinical impression of obstructive jaundice. After two normal radioactive-fat studies surgery was not advised. The patient improved, and her jaundice gradually disappeared. Prior to discharge it was learned that chlorpromazine (Thorazine) had been administered to her for several weeks before her admission, and it was felt that this adequately explained the entire picture.

Comment

Sufficient evidence appears to be at hand to establish the validity of the radioactive triolein technique as a means to detect and quantitate abnormalities in fat absorption.[4,5]

More recently, Van Handel and Zilversmit[6] have offered additional confirmatory data. They have shown that after ingestion of a test meal containing I^{131} triolein plus cottonseed oil the radioactive fat appeared to follow the same fate as the carrier fat. The appearance and disappearance of the radioactive triglycerides in the plasma agreed closely with the chemical determinations of these substances.

There is less agreement, however, as to what fraction of the blood to count—whole blood, serum, or a trichloracetic acid precipitate which contains only the lipid-bound I^{131}. In spite of these variances in technique, the format of the curves obtained is very similiar, and one curve may often be superimposed upon another, although quantitative comparisons are more difficult.

We have measured the whole-blood radioactivity in an attempt to simplify the procedure and feel that at least over the ascending limb of the curve this reflects absorption, since the radioactivity in the blood must have come from the originally ingested triolein.

On a clinical level there is also enough information available to allow a preliminary evaluation of this procedure.

Beres,[5] McKenna,[7] and Shingleton[8] and their groups have had large experiences with this technique. They have reported favorably and have obtained good correlation with stool studies and other fat-tolerance tests. More recently Fierst has shown that a good relationship exists between the RAF studies and vitamin A absorption curves.[9]

Summary of Fat Absorption Studies with I^{131} Triolein

	Sum of 4-, 5-, 6-Hr. Absorption Values (Mean)
Normal	45.4
Duodenal ulcer	44.5
Irritable-bowel syndrome	39.8
Subtotal gastrectomy	41.6
Chronic pancreatitis	19.0
Sprue	5.3
Cirrhosis	39.0
Extrahepatic obstructive jaundice	10.1
Nonobstructive jaundice	30.5

In the interpretation of our data four factors appear to have significance: (1) the sum of the fourth-, fifth-, and sixth-hour blood radioactivity values; (2) the time at which peak absorption occurs; (3) the magnitude of this peak value, and (4) the rate of disappearance of activity from the blood.

The fourth- to sixth-hour absorption sum is a convenient way to compare results on a semiquantitative basis. In the Table we have summarized all of our results according to this schema. If this sum value is below normal, we then note the magnitude of the peak value of the curve. If this too is significantly low, we are satisfied that some impairment of fat absorption exists. If, however, the blood radioactivity at this peak hour is within the normal range, we report that fat absorption is normal, regardless of the low summation. We have observed this on several occasions with no ready explanation forthcoming (Fig. 9). Delayed gastric emptying was ruled out by x-ray studies. We have tentatively assummed that a delay in small intestinal motility has been responsible. In these instances, reliance on the four- to six-hour absorption levels would have led to an erroneous conclusion. Therefore we routinely continue to measure serial blood samples after ingestion of the test meal until a peak is reached.

The time at which the blood radioactivity is maximum after ingestion of the tagged triolein is affected by various things, most important of which is the rate of gastric emptying.[10] Since fat is a potent inhibitor of motility, it is readily understood how the various test meals in use at the present time, with their varying compositions, would lead to varying results. In our studies the blood radioactivity usually reached a maximum between the fifth and sixth hours. Rapid gastric emptying as seen in patients following a subtotal gastrectomy was reflected by an absorption curve, in which the peak value occurs sooner than normal but is lower than normal. Thereafter the curve flattens out and then drops off (Fig. 10).

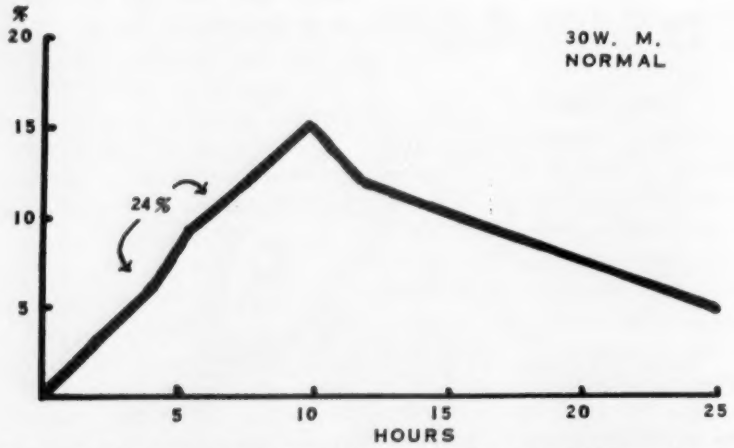


Fig. 9.—I^{131}-labeled fat. Low 4th- to 6th-hour absorption value, with normal peak value at 10th hour.

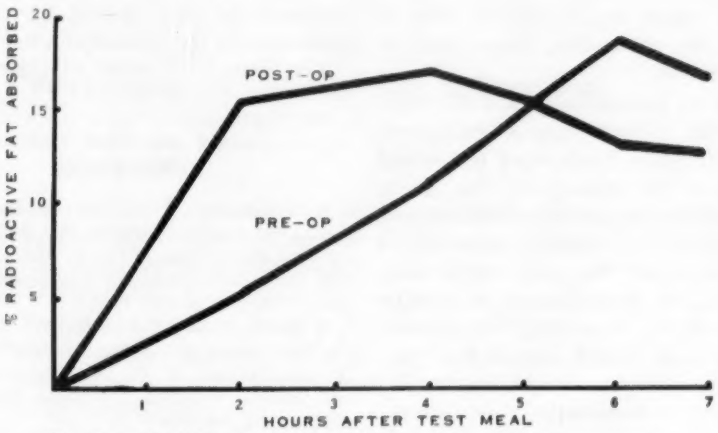


Fig. 10.—I^{131} triolein absorption before and after subtotal gastrectomy.

The rate of disappearance of the blood radioactivity is much more difficult to interpret. Here the factors of utilization, transport, storage, and excretion are all participating, so that whole blood measurements may be misleading. We are at present making simultaneous determinations of the activity of the lipid-bearing portion and the inorganic fraction as well as the whole blood. Thus far it appears that the normal ratio of inorganic to organic radioactivity is altered in patients with hyperlipemia and coronary artery disease.

Urinary radioactivity studies are inconclusive at present. In general they have paralleled the absorption curves.

The I^{131} in the urine is present as inorganic iodide, and as such it represents the net result of many processes concerned with the metabolism of the orally administered fat. As such it should be some reflection of the rate of utilization of the fat, so that fractional analyses in combination with the blood ratios mentioned previously may prove to be more informative.

We have performed only a few fecal radioactivity excretion studies, and these have been in accord with the blood absorptive patterns. It should be pointed out that a 6-hour blood curve is merely a measure of the rate of absorption over a 6-hour period and is hardly equivalent to a 48- or 72-hour stool study. Thus poor correlation between these two methods must be expected in some cases. All of the patients we are studying are in a dynamic state, so that the blood values indicate a trend only at that specific time. It is not inconceivable that in cases where a flat absorption curve was obtained with a normal 48- or 72-hour stool specimen that certain alterations occurred after the 6th hour which allowed for normal fat absorption thereafter. For example, in obstructive jaundice the obstruction may relieve itself after the blood-activity portion of the test has been completed with resultant normal fat absorption. Thus we believe that many of the discrepancies noted by others may be resolved if analyzed more critically. In our experience a low or flat absorption curve when associated with a subnormal peak value has invariably been indicative of an abnormal state.

The RAF procedure has also found use in several other ways. It is possible to determine the improvement in fat absorption after treatment, such as in sprue following corticoid therapy, and in congestive failure after compensation has been restored. Substances such as si-

tosterols, which are supposedly able to decrease fat absorption, may also be readily studied.

It must be remembered that this technique is not without certain limitations. A flat absorption curve does not reveal anything of the etiology of the defect, which may be primarily mucosal or due to a lack of bile or pancreatic enzymes. A normal curve, on the other hand, fairly well rules out the existence of a major degree of any of these, although a minor deficiency may escape detection.

Summary

Whole-blood radioactivity measurements after a test meal containing I^{131}-labeled triolein is a simple method to study fat absorption and gives informative and reliable results. The procedure is easily applicable to even the smallest hospital with an isotope laboratory and usually obviates the need for more difficult techniques, such as stool balance studies, chylomicron counts, and vitamin A tolerance tests.

Proper interpretation of the absorptive patterns requires that serial blood radioactivity determinations be made until a peak value occurs. In the average case, however, the sum of the fourth-, fifth-, and sixth-hour values will give ample evidence as to the presence or absence of an absorption defect.

Preliminary studies in patients with jaundice indicate that the test may be of value in distinguishing the various types, characteristic curves being obtained in obstructive and nonobstructive jaundice.

Further determinations of the ratio of inorganic to organic blood radioactivity correlated with urinary excretion results may give additional insight to the fate of ingested fat and should be especially applicable to the process of atherogenesis.

Miss Hettie Brenz, isotope technician, helped in this study.

101 S. 20th St. (3).

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The Prevention of Myocardial Infarction

BENJAMIN MANCHESTER, M.D., Washington, D. C.

Recent advances in the management of acute myocardial infarction have improved the immediate prognosis for recovery. Early diagnosis of less severe cases accounts, in part, for the mortality decline. Progress in current therapy is responsible for the large number whose recovery enables them to resume a useful and productive life.

The family of the patient with acute coronary occlusion can now be reassured that the vast majority of persons so afflicted recover.[1] The over-all mortality during the acute attack of 15% to 25% is in sharp contrast with the earlier incidence of 50% to 60%.[2] Uncomplicated first attacks are reported with a fatality rate of 3.4% to 8.5%.[3-5] Such data support the optimism of physicians for the favorable immediate prognosis.

However, long-term prognosis of subsequent myocardial infarction is unpredictable. The variability in the natural course of the disease has made the long-term outlook uncertain. While one may live 20 years after the initial occlusion, another may die suddenly. Both represent clinical extremes of the disease. It is impossible to predict the course the disease will follow. The physician is therefore faced with the paramount problem as to what therapeutic regimen is available to prevent subsequent myocardial infarction.

The purpose of this report is to present my experience with continuous long-term anticoagulant therapy for the prevention of subsequent coronary thrombosis and cardiac infarction. The observations were made over a period of from 1 to 10 years in 712 patients with one or more myocardial infarctions prior to this study. The incidence of subsequent myocardial infarction, congestive heart failure, angina pectoris, thromboembolic complications, and survival by patient-years were observed in the control, anticoagulant, and "untreated" groups.

Material and Methods

All patients were first seen and followed during an acute episode of myocardial infarction, confirmed clinically and electrocardiographically. Alternate patients received an oral anticoagulant and ascorbic acid, while the control received a placebo of ascorbic acid, 250 mg. daily. The result of anticoagulant therapy in acute myocardial infarction in the first 500 patients was previously reported.[6]

After the recovery from the acute infarct, both the control group and the anticoagulant group were encouraged to have blood prothrombin determinations by my capillary blood prothrombin test at intervals of one to four weeks. The blood prothrombin time was maintained at 25 to 35 seconds (normal, 14 to 18 seconds ± 2.5 seconds). The same personnel followed the patients.

Except for oral anticoagulants, bishydroxycoumarin (Dicumarol) or acenocoumarin (Sintrom), both groups received the same medical care, dietary regimen, and digitalis, diuretics, and/or sedatives as required. The number of visits and laboratory procedures were equal and rigidly adhered to. Those who failed to submit to a blood prothrombin determination at least once a month or who failed to continue the placebo or anticoagulant were rejected from the study.

After 10 years there remained 404 patients who had cooperated and continued uninterruptedly the medical regimen outlined above. The majority, 329, were private patients; 75 were clinic patients. Two hundred four have continued to take oral anticoagulants (bishydroxycoumarin or acenocoumarin) from 1 to 10 years, and two hundred were maintained with the placebo of ascorbic acid.

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From the George Washington University School of Medicine and the Medical Service, District of Columbia General Hospital. Assistant Clinical Professor of Medicine, George Washington University, School of Medicine.

TABLE 1.—*Composition of Study for the Prevention of Subsequent Myocardial Infarction* *

	Anticoagulant Group (204)		Control Group (200)		Untreated (157)	
Mean age, yr.	58		59		61	
Range	31-92		39-88		44-81	
	No.	Per Cent	No.	Per Cent	No.	Per Cent
Sex						
Male	156	76.4	148	74.0	109	69.4
Female	48	23.5	52	26.0	48	30.5
Two or more infarctions	51	25.0	40	20.0	28	17.8
Poor risk	151	74.1	143	71.5	41	26.1
Good risk	53	25.9	57	28.5	116	73.8
Digitalized	32	15.6	66	33.0	24	15.2

* Observed 1-10 yr.

Included in the control group are 23 who did not wish to continue taking anticoagulants after recovery from the acute infarction. Only patients who continued to take anticoagulants during the acute illness were allowed to continue the prolonged therapy. The role of cooperation, number of visits, and selection of patients were rigidly followed for both groups. Of the remaining 308 there are 157 available for follow-up and comparison; they are referred to as the "untreated" group and serve as another control.

Results

The composition of the group is shown in Table 1. There were 204 patients in the anticoagulant group, 200 in the control group, and 157 in the untreated group. The mean ages in years were 58, 59, and 61, respectively; the range was 31-92 in the anticoagulant, 39-88 in the control group, 41-81 in the untreated group. In the anticoagulant, 156 (76.4%); in the control, 148 (74%), and in the untreated, 109 (69.4%) were men, and 48 (23.5%), 52 (26%), and 48 (30.5%), respectively, were women.

Previous infarction was noted in 51 (25%) in the anticoagulant group, in 40 (20%) in the control group, and 28 (17.8%) in the untreated group. In the anticoagulant group 151 (74.1%) were poor risk and 53 (25.9%) were good risk. In the control group 143 (71.5%) were poor risk and 57 (28.5%) were good risk. In the untreated group 41 (26.1%) were poor risk and 116 (73.8%) were good risk. There were 32 (15.6%) digitalized in the anticoagulant group, 66 (33%) in the control group, and 24 (15.2%) in the untreated group.

Subsequent myocardial infarction in the anticoagulant group occurred in 29 (14.2%), with a mortality of 6 (20.6%). In the control group the incidence was 68 (34%), with a mortality of 36 (53%). In the untreated group the incidence was 63 (40.1%), with a mortality of 35 (55.5%).

Cardiac decompensation in the anticoagulant group developed in 43 (19.7%); 8 (18.6%) died. In the control group heart failure developed in 72 (36%) and 33 (45.8%) died. In the untreated group 71 (45.2%) developed decompensation and 41 (57.7%) died.

Thromboembolic complications in the anticoagulant group were 14 (5.8%), with a mortality of 2 (14.2%). In the control group there were 35 (17.5%) and the mor-

TABLE 2.—*Incidence and Mortality of Subsequent Complications* *

Subsequent Complications	Anticoagulant (204)				Control (200)				Untreated (157)			
	Incidence		Mortality		Incidence		Mortality		Incidence		Mortality	
	No.	Per Cent	No.	Per Cent	No.	Per Cent	No.	Per Cent	No.	Per Cent	No.	Per Cent
Myocardial infarction	29	14.2	6	20.6	68	34	36	53	63	40.1	35	55.5
Cardiac decompensation	43	19.7	8	18.6	72	36	33	45.8	71	45.2	41	57.7
Thromboembolic complications	14	5.8	2	14.2	35	17.5	16	45.7	Undetermined			
Hemorrhage	6	2.9	0	0	0	0	0	0	0		0	0
Total	92	45.09	16	7.8	175	87.5	85	42.5	134	85.3	76	48.4

* 1–10 yr.

TABLE 3.—*Year, Incidence, and Mortality of Subsequent Myocardial Infarction*

Yr.	Anticoagulant (204)		Control (200)		Untreated (157)	
	Incidence	Mortality	Incidence	Mortality	Incidence	Mortality
1	1	1	8	5	7	4
2	1	0	9	4	12	5
3	5	1	7	4	6	3
4	3	1	12	7	10	6
5	3	1	5	2	6	4
6	4	0	4	2	4	2
7	3	0	4	2	7	6
8	3	0	8	5	4	2
9	4	1	6	3	3	1
10	2	1	5	2	4	2
Total	29 (14.2%)	6 (20.6%)	68 (34%)	36 (53%)	63 (40.11%)	35 (55.5%)

tality was 16 (45.7%). No data are available in the untreated group.

Hemorrhagic complications occurred only in the anticoagulant group. There were six (2.9%) without any fatality (Table 2).

The year, incidence, and mortality of subsequent myocardial infarction are shown in Table 3. The first five years, in the control and untreated groups, show the highest incidence of subsequent myocardial infarction as 41 (60% and 65%, respectively) and the mortality as 22 (53% for both). In the anticoagulant group the incidence of subsequent infarction was 13 (44%) and mortality was 4 (30%).

The incidence of subsequent myocardial infarction and mortality was greater between the ages of 46 and 65 for all groups. The mortality rate in subsequent infarction was two to three times greater in the control than in the anticoagulant group (Table 4).

The development of angina pectoris subsequent to myocardial infarction was the same. In the anticoagulant group there were 74 (36.2%), and in the control, 72 (36%). In the anticoagulant group 38 (51.3%) showed improvement by increased tolerance in walking and performing the Masters' two-step test. In the control 20 (27.5%) showed improvement. In the anticoagulant series there were 4 (5.4%) deaths; in the control series there were 30 (41.6%). In the untreated group data on the incidence of angina pectoris were not available (Table 5).

Thromboembolic complications, exclusive of myocardial infarction, are shown in Table 6. In the anticoagulant group pulmonary emboli occurred in 8 (3.9%) without a mortality; in the control group there were 21 (10.5%), with a mortality of 7 (33%). In the anticoagulant group cerebral emboli were present in 3 (1.5%); 2 (67.2%) died. In the control group there were 8 (4.0%), and 6 (75%) died. Phlebitis occurred in the anticoagulant group in 3 (1.5%); in the control group, in 6 (3.0%), without mortality in either group. In the untreated group there is no information available.

TABLE 4.—*Age and Mortality of Subsequent Myocardial Infarction*

Age	Anticoagulant			Control			Untreated		
	Cases	Mortality	Per Cent	Cases	Mortality	Per Cent	Cases	Mortality	Per Cent
Up to 45	7	1	14.2	17	7	41	5	3	60
46–55	10	2	20	18	5	27	24	9	37.5
56–65	8	2	25	22	15	68	23	14	60.8
Over 65	4	1	25	11	9	81.8	11	9	81.8
Total	29 (14.2%)	6	20.6	68 (34%)	36	53	63 (40.1%)	35	55.5

The effect of anticoagulant therapy on patient-years of known recurrence and survival is shown in Table 7. It will be noted that the total patient-years of survival in the anticoagulant group was 1064; there was 808 patient-years of survival in the control groups, and 658.5 patient-years of survival in the untreated group. In the anticoagulant group there were 2.73 subsequent infarctions per 100 patient-years and 0.56 deaths

TABLE 5.—*Course of Angina Pectoris on Continuous Long-Term Anticoagulant Therapy*

	Anticoagulant	Control	Untreated
Angina	74 (36.2%)	72 (36%)	Data not available
Improved	38 (51.3%)	20 (27.5%)	Data not available
Died	4 (5.4%)	30 (41.6%)	Data not available

TABLE 6.—*Site of Thromboembolic Complications* *

	Anticoagulant		Control		Untreated	
	Cases	Mortality	Cases	Mortality	Cases	Mortality
Pulmonary emboli	8	0	21	7 (30%)	Data not available	
Cerebral emboli	3	2 (66.6%)	8	6 (75%)	Data not available	
Phlebitis	3	0	6	0	Data not available	

* Exclusive of myocardial infarction.

per 100 patient-years. In the control group there were 8.42 subsequent infarctions per 100 patient-years and 4.45 deaths per 100 patient-years. In the untreated group there were 9.6 subsequent infarctions per 100 patient-years and 5.3 deaths per 100 patient-years. The number of subsequent infarctions was three times greater in the control group, and the mortality rate was eight times greater than in the anticoagulant series.

Comment

After the recovery from the myocardial infarction due to coronary thrombosis the patient must adjust to a new way of life. In essence it is a moderation in living, with restrictions, interdictions, and prescriptions. The regimen is designed to alleviate or prevent discomfort due to coronary insufficiency or to maintain or restore cardiac efficiency and compensation. The need for amelioration of symptoms is further evidence of the relentless progress of the degenerative disorder. Such efforts provide symptomatic relief but do not prevent or retard the pathogenesis of atherosclerosis.

The benefits accrued through reduction in weight and a moderation of activity and habits may prevent the onset of angina pectoris or heart failure. There is, however, no evidence that the interdictions or prescriptions serve to prevent subsequent myocardial infarction. It is apparent that even such devotion to well-being is no guarantee to being well.

After the recovery from acute myocardial infarction, whether mild or severe, good or poor risk, subsequent recurrence is inevitable. Coronary thrombosis in midlife has become Public Health Problem Number One. It is the chief cause of death after the age of 40.

The present experience of continuous (1 to 10 years) long-term anticoagulant therapy in 204 persons compared with an alternate 200 control patients and 157 untreated patients has proved effective in preventing subsequent myocardial infarction and increased patient-year survival.

Such therapy is practical, feasible, and economical. The use of a simple capillary blood prothrombin test employed in the present series made the management inexpensive and practical.

Levine [2] noted a 25% mortality in the first year and 50% in the second year, and 75%

TABLE 7.—*Effect of Anticoagulant Therapy on Patient-Years of Nonrecurrence and Survival*

	Anticoagulant Group				Control Group				Untreated Group			
Yr. of Observation	Total Cases	Subsequent Infarctions	Deaths	Patient-Yr. of Survival	Total Cases	Subsequent Infarctions	Deaths	Patient-Yr. of Survival	Total Cases	Subsequent Infarctions	Deaths	Patient-Yr. of Survival
(Y)	(C)		(D)	(Y×C−D/2)	(C)		(D)	(Y×C−D/2)	(C)		(D)	(T×C−D/2)
1	23	1	1	22.5	41	8	5	38.5	32	7	4	30
2	20	1	0	40	30	9	4	58	20	12	5	37.5
3	22	5	1	65.5	28	7	4	82	21	6	3	61.5
4	21	3	1	83.5	20	12	7	76.5	17	10	6	65
5	20	3	1	99.5	18	5	2	89	11	6	4	53
6	26	4	0	156	17	4	2	101	17	4	2	101
7	21	3	0	147	18	4	2	125	15	7	6	102
8	20	3	0	160	15	8	5	117.5	11	4	2	87
9	19	4	1	170.5	7	6	3	61.5	7	3	1	62.5
10	12	2	1	119.5	6	5	2	59	6	4	2	59
Total	204	29	6	1,064	200	68	36	808	157	63	35	658.5
Rate/100 patient yr.		2.73	0.56			8.42	4.45			9.6	5.3	

did not live beyond five years. Angina pectoris was noted in 66%, and 25% manifested congestive heart failure. Bland and White [12] noted a 75% mortality within 10 years. Smith [13] observed a 25% mortality within the first year after myocardial infarction. These statistics do not permit complacency or expectant care of complications as they develop. Although extensive investigation in the pathogenesis of atherosclerosis continues, there is as yet no acceptable specific treatment of coronary atherosclerosis.

The successful reduction of mortality and thromboembolic complications in acute myocardial infarctions by anticoagulants has justified the trial of continuous long-term anticoagulation. The present report of prolonged anticoagulant therapy in 204 patients compared with 200 controls and 157 untreated confirms the favorable results of earlier investigators.[6-10]

The present results of long-term anticoagulant therapy indicate that the grave prognosis noted above after subsequent myocardial infarction can be prevented by continuous long-term anticoagulant therapy.

The incidence of subsequent myocardial infarction in the anticoagulant group was one-third of the control, while the mortality rate in the control series was eight times as great as that of the anticoagulant group. Although the incidence of subsequent infarction and thromboembolic complications was greatly reduced in the anticoagulant group, the occurrence indicates the limitations of presently available oral anticoagulants. Bishydroxycoumarin was employed in the earlier part of the study; during the past 30 months acenocoumarin has been used exclusively as the oral anticoagulant. Its sustained antithrombotic effect, predictable dosage response, and ease of administration have recommended it as a desirable agent for long-term therapy.

Although oral anticoagulants are known to influence the prothrombin activity and Factors V and VII, in some persons other facets of the clotting mechanism may predominate and thus account for the thromboembolic events in the anticoagulant series.

The improvement in angina pectoris in the anticoagulant group can only provoke speculation. The idea that increased coronary blood flow is due to lessened blood viscosities has been offered by Nichol and Fassett.[7] Gilbert and Nalefski [14] have attributed the decrease in anginal pain to the profound vasodilatation of the coronary arteries. The role of frequent visits and repeated observations as a psychotherapeutic measure cannot account for the reduced anginal pain, since both the control and the anticoagulant group were seen an equal number of times with the same degree of attention.

The greatest deterrent to the use of anticoagulant therapy has been the fear of hemorrhage. The present report demonstrates that continuous (1 to 10 years) long-term anticoagulant therapy is feasible and safe. The incidence of bleeding was 2.9%. The administration of phytonadione (vitamin K_1) oxide intravenously corrected the hypoprothrombinemia without hospitalization. The danger from bleeding is far less than the danger associated with the inherent hazard of subsequent myocardial infarction.

A simple capillary blood prothrombin test has proved accurate, inexpensive, and convenient for the regulation of dosage in the maintenance of antithrombotic blood levels. Trauma from repeated venopunctures is avoided. The prothrombin time of 25-35 seconds is equivalent to the Quick 30%-50% of prothrombin activity. It has been maintained at this level by others and found to be effective in preventing intravascular thrombosis and at the same time reducing the hazard of hemorrhage.

At the suggestion of Link the addition of 250 mg. of ascorbic acid was administered to reduce vascular fragility and maintain normal blood ascorbic acid level and thereby reduce the tendency to bleeding. Clinically the present experience justifies the addition of ascorbic acid (vitamin C) whenever oral anticoagulants are employed.

The indications for continuous long-term anticoagulant therapy must be individualized. It cannot be prescribed for all patients after recovery from acute myocardial infarction. However, the development of a thromboembolic complication is a positive indication for such therapy. The prevention of a subsequent infarction in a young person with a familial history is another instance for continuous anticoagulant treatment. The duration for maintaining such treatment cannot be generalized.

There are definite prerequisites in the selection for continuous long-term anticoagulant therapy. A cooperative patient is essential. An irresponsible or incompetent person is not a suitable candidate for such therapy. The physician who is not meticulous to detail or lacks the appreciation of blood prothrombin determinations and/or the pharmacology of the oral anticoagulants may render anticoagulant therapy less effective.

Conclusions

The incidence of subsequent infarction was three times greater in the control and untreated groups; the mortality rate was eight times more in the control and untreated than in the anticoagulant group.

Continuous long-term anticoagulant therapy is a significant advance in the prevention of subsequent coronary thrombosis. The results provide evidence that such therapy may prolong life and productivity. For the man in the street who associates "heart attacks" with sudden death, abbreviated life span, or invalidism, this report provides a more optimistic outlook for the future.

3200 Sixteen St., N. W. (12).

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The Pulmonary Obstruction Syndrome in Schistosoma Mansoni Pulmonary Endarteritis

Report of Five Cases

ERNESTO J. MARCHAND, M.D.; RAÚL A. MARCIAL-ROJAS, M.D.; ROBERTO RODRÍGUEZ, M.D.; GERARDO POLANCO, M.D., and R. S. DÍAZ-RIVERA, M.D., San Juan, P. R.

It has been known for many years that infection caused by Schistosoma affects the lungs, but its frequency and importance have received scanty recognition. Dr. Díaz-Rivera and co-workers [1] reported their observations on 12 patients suffering from acute schistosomiasis during the period of maturation and oviposition. They emphasized the explosive gastrointestinal and pulmonary manifestations, clinically confused with various dysenteric diseases, bronchopneumonia, and pulmonary infiltrative eosinophilia. The latter picture suggests a hypersensitivity state as the chief factor governing the clinical and pathological manifestations.

Belleli, of Alexandria, reported the first case of ova in the lungs in a patient suffering from disease caused by Schistosoma haematobium.[2] Azmy Bey in Cairo, reported the first two cases of schistosomal cor pulmonale that at postmortem showed a pulmonary arteriosclerosis.[3] The pathogenesis of schistosomal pulmonary obstruction syndrome was discussed by Shaw and Ghareeb, in 1938,[4] and Lopes de Faria, in 1952.[5] Since the report by Kenawy, from Cairo, on the clinical aspects of cor pulmonale in seven patients with schistosomiasis,[6] the Egyptian physician is becoming more aware of the pulmonary manifestations of Schistosoma infection, and the hemodynamic consequences, similar to essential pulmonary hypertension,[7] are being investigated.

The pathological lesion in the lungs responsible for this clinical syndrome is a widespread obliterative arteriolitis caused by repeated reinfection of the arterioles by the ova. The pathophysiology consists chiefly of repeated ova emboli into the pulmonary arterioles. For many years it has been postulated that these ova emboli came from the gastrointestinal tract through the systemic and/or the collateral circulation. However, there is enough experimental work proving that these ova emboli may also reach the lungs from the gastrointestinal tract via vascular shunts in the liver. The existence of arteriovenous or venous-venous communications in the liver, 50μ to 180μ in diameter, were shown by the studies of Joseph D. Mann on the vasculature of the human liver, using the injection-cast method,[8] and the experiment of Prinzmetal, involving the injection of glass spheres into an afferent blood vessel (portal vein) and their recovery from efferent blood vessel (hepatic vein).[9] Because of tissue hypersensitivity state a widespread arteriolitis develops which gradually leads to marked rise in precapillary pulmonary pressure, hypertrophy ot the right ventricle, and eventually right-sided heart failure.

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Associate Professor of Clinical Medicine, University of Puerto Rico School of Medicine (Dr. Marchand); from the Department of Pathology of the University of Puerto Rico School of Medicine and the I. González Martínez Oncologic Hospital (Dr. Marcial-Rojas); Instructor in Medicine, University of Puerto Rico School of Medicine (Dr. Rodríguez); from the Department of Pathology, Bayamón District Hospital (Department of Health) (Dr. Polanco); Professor of Medicine, University of Puerto Rico School of Medicine (Dr. Díaz-Rivera).

Characteristically, these patients are young adults from areas endemic for schistosomiasis, with no history of chronic bronchopulmonary disease. On examination the respiratory distress of the patient is out of proportion to the scanty pulmonary findings. The clinical features of dyspnea associated with outstanding cardiac findings are confused with rheumatic fever and congenital heart disease.

The purpose of the present paper is to report our observation of five patients with schistosomal cor pulmonale. The diagnostic challenge presented by this condition appears to concern not only the physician in areas endemic for schistosomiasis but also those practicing in other countries where an increasing percentage of the population are immigrants. This situation exists in the United States, with approximately 1,000,000 inhabitants from Puerto Rico, where Manson's schistosomiasis has been found in 11% of the population.

Report of Cases

CASE 1 (Bayamón District Hospital).—A 20-year-old white youth was admitted to the hospital on Dec. 7, 1954, complaining of exertional dyspnea, generalized weakness, and ankle edema of eight months' duration. There was no history of cyanosis or cardiac symptoms during his childhood, but two years prior to this admission he had pain on his right knee, extending all the way up to the thigh. His pain was accompanied by redness and heat and lasted about three weeks. He recovered from this episode and felt well until eight months prior to admission, when he went to see a private physician because of progressive exertional dyspnea, generalized weakness, and ankle edema, which interfered with his work as a laborer. He was told that he had a large liver and spleen. There was no history of jaundice, hemoptysis, or abdominal pain. Since his symptoms became progressively worse, he came to the hospital for treatment. The past medical history and family history were not contributory.

Physical examination revealed a well-developed and well-nourished white youth of about 20 years of age in mild respiratory distress, with a peculiar cyanotic hue of the cheeks and mild cyanosis of the lips and ear lobes. The blood pressure was 130/90; pulse, 96 per minute; respirations, 24 per minute, and temperature, 99.3 F (37.4 C). There was a slight icteric tinge to the conjunctivae. The trachea was in the midline, and the thyroid was not enlarged. There was marked congestion of neck veins. The thorax was normal in outline. The respiratory excursions were equal bilaterally. The lungs were clear to percussion and auscultation. While resting quietly in the sitting position for a few minutes the patient showed engorged neck vessels, cyanosis of lips and ear lobes, but no dyspnea. Examination of the heart revealed heaving pulsations in the precordium. A systolic thrill was palpable over the third left intercostal space close to the sternum. Cardiac dulness was close to the anterior axillary line and increase in the third left intercostal space. There was a regular rhythm and a diffuse moderately loud systolic murmur, loudest in the mitral area; the pulmonic second sound was very loud and split. The liver was felt 3 fingerbreadths below the right costal margin and was slightly tender to palpation. The spleen was enlarged to 3 fingerbreadths below the left costal margin. There was no ascites. The external genitalia and the findings on rectal examination were normal. A 2+ pitting leg edema was present. There were no palmar erythema nor spider nevi.

Laboratory studies revealed WBC, 6440 per cubic millimeter; RBC, 4,100,000 per cubic millimeter, and hemoglobin, 13.3 gm. per 100 cc. Urinalysis: specific gravity 1.008; 1+ albumin; negative for sugar; microscopic examination, negative. VDRL, negative; prothrombin time, 19 seconds, control, 15 seconds; NPN, 32 mg. per 100 cc.; BUN, 13.25 mg. per 100 cc. Stools were positive for occult blood, Ancylostoma, Trichuris, and S. mansoni ova. The rectal biopsy specimen was revealed to be loaded with S. mansoni ova. Sedimentation rate, 25 mm. in one hour; volume of packed cells, 45%; serum bilirubin, 1.1 mg. per 100 cc. direct and 1.5 mg. per 100 cc. total; total protein, 5.9 gm. per 100 cc., with albumin, 3.7, and globulin, 2.2 gm. per 100 cc. Thymol turbidity, 5.4 units; cephalin flocculation test, 3+; sulfobromophthalein test, 32% of dye retained in 45 minutes (patient was slightly jaundiced). The bleeding and clotting time were normal. Venous pressure was 180 mm. of H_2O, and with pressure over the liver it increased to 200 mm. of H_2O.

The electrocardiogram showed a QRS electrical axis of +108 degrees; sinus rhythm, 108; P-R interval, 0.16 seconds; QRS, 0.05 seconds, with a Q-T interval of 0.25 seconds, marked clockwise rotation on the longitudinal axis, right ventricular hypertrophy, and suggestive left ventricular hypertrophy and incomplete right bundle-branch block.

X-ray of the chest was reported as follows: The lung fields are clear. The hilar vessels are prominent; the peripheral vascular markings are within normal limits. The heart is moderately enlarged in its transverse diameter, especially to the left. The left border is convex and shows a low

apex. The pulmonary artery segment is moderately prominent, and the aortic knob is small in size. There is some discrepancy between the main pulmonary artery and the relative avascularity of the lung fields.

The course in the hospital was as follows: The patient was fairly well until Dec. 14, 1955, when he passed about 500 cc. of tarry stools streaked with red blood and vomited about 100 cc. of red blood. A Sengstaken Blakemore tube was inserted in place, and the patient was given a transfusion of 1000 cc. of whole blood after being digitalized. On Dec. 17, 1955, the patient was taken to the operating room for ligation of the esophageal varices, and while at the operating table he had a cardiac standstill which was refractory to all treatment.

Comment.—A 20-year-old white youth from an area endemic for schistosomiasis went into cardiac failure eight months prior to admission to the hospital. On admission the most important findings were moderate dyspnea, slight cyanosis, no gross pulmonary findings, but outstanding cardiovascular findings of cardiomegaly, evidence of pulmonary artery hypertension characterized by a very loud second pulmonic sound, and hepatosplenomegaly. Roentgenogram of the chest showed a moderately enlarged heart with a prominent pulmonary artery segment and an avascular peripheral field. The electrocardiogram demonstrated incomplete right bundle-branch block and right ventricle hypertrophy. These findings suggested pulmonary heart disease with the obstructive pathology in the arterioles. The presence of hepatosplenomegaly plus positive stool and rectal biopsy for S. mansoni ova made the etiological diagnosis antemortem. It is of interest to note that this patient died in cardiac arrest, since it has been noticed that patients with schistosomal cor pulmonale do not tolerate surgical intervention well.

CASE 2 (Río Piedras Municipal Hospital).—A 45-year-old white woman was admitted to the hospital for the first time on June 20, 1952, complaining of generalized weakness and ankle edema of four days' duration but no dyspnea. She denied any history of hematemesis, tarry stools, dyspnea, orthopnea, or cyanosis. Pertinent physical findings were limited to the heart and lungs. On admission her blood pressure was 150/90 mm. of Hg; pulse, 100 per minute; respirations, 25 per minute; temperature, 98 F. There were few moist rales on both lung fields. The point of maximal cardiac impulse was at the sixth left intercostal space. There was a thrill at the third left intercostal space close to the sternum and a loud systolic murmur and a faint diastolic murmur at the pulmonic area. A 2+ pitting edema of the legs was present. Laboratory studies revealed RBC 4,210,000 per cubic millimeter; hemoglobin, 12.6 gm. per 100 cc; WBC, 4100 per cubic millimeter with 59% neutrophils, 34% lymphocytes, and 7% eosinophils. Results of urinalysis were normal. The stools showed Necator americanus ova. X-ray of the chest showed hilar congestion, rather clear peripheral lung fields, and a marked prominence of the pulmonary artery segment. Impression: idiopathic dilatation of pulmonary artery.

The patient was given a low salt diet and was discharged seven days after hospitalization with marked improvement of her general health.

She was readmitted on Sept. 8, 1952, with the chief complaints of chills, fever, icterus, and dark urine of nine days' duration. She claimed that after being discharged she had felt well, except for occasional precordial pain and palpitations, until nine days prior to admission, when she developed chills, fever, generalized weakness, swelling of her face and legs, pain in the right upper quadrant, icterus, and dark urine. She denied any history of cough, diarrhea, hematemesis, tarry stools, dysuria, hematuria, or costovertebral angle tenderness. While the admission history was being taken her respiratory excursions became very shallow and her heart beats became inaudible. Artificial respiration and nikethamide (Coramine) were given, and the patient responded well.

Physical examination revealed a well-developed well-nourished 45-year-old white woman severely dyspneic and having jaundice. The blood pressure was 80/45 mm. of Hg; pulse, 86; respirations, 42 per minute, and temperature, 98.2 F. The eyes were icteric, and the pupils reacted normally to light but not to accommodation. The tongue was coated, and the nasopharynx was markedly red. The cervical veins were moderately distended. There was dullness in both bases and moist rales throughout both lungs.

Examination of the heart revealed the P. M. I. in the sixth left intercostal space, a thrill in the pulmonic area, a gallop rhythm, and loud systolic and diastolic murmurs at the third left intercostal space. The liver was felt 3 fingerbreadths below the right costal margin, and the spleen, 3 fingerbreadths below the left costal margin. No ascites could be detected. There was a 2+ pitting edema of the lower extremities. The skin was slightly icteric, but spider nevi were not present.

Laboratory tests on admission revealed RBC, 4,600,000 per cubic millimeter; hemoglobin, 13.9 gm. per 100 cc.; WBC, 14,900 per cubic millimeter,

with 90% neutrophils and 10% lymphocytes. The urine gave a 2+ reaction to albumin and contained 5-7 WBC and 4-5 RBC per high-power field. The total serum bilirubin was 10.2 mg. per 100 cc., with 7.4 mg. per 100 cc. in one minute. The blood sugar was 134.6 mg. per 100 cc., and the NPN, 63 mg. per 100 cc. Stool examination showed Trichuris. The Kahn test was positive. Roentgenogram of the chest was interpreted as showing marked pulmonary congestion. The electrocardiogram showed again a right axis deviation and right ventricular hypertrophy.

The patient was digitalized at the hospital, with slight improvement of her condition. She signed out from the hospital six days after admission and died at home five days afterward.

Comment.—This 45-year-old white woman was admitted to the hospital three days after the onset of symptoms of congestive heart failure. On physical examination she revealed a loud systolic and diastolic murmur over the pulmonic area, with scanty lung findings and edema of the lower extremities. Undoubtedly the examiner overlooked the presence of hepatosplenomegaly in the first admission. X-rays of the chest revealed an aneurysmal dilatation of the pulmonary artery, with rather clear peripheral vascular fields. A worldwide-known cardiologist saw this patient in consultation and made a diagnosis of pulmonary stenosis with poststenotic dilatation. This is a rather frequent diagnostic mistake in these cases. Another case not included in this series was diagnosed as a Lutembacher's syndrome, and Case 4 was thought to have interatrial septal defect. This case also illustrates the rather fast downhill course these patients have once cardiac failure develops.

CASE 3 (San Juan City Hospital).—A 19-year-old white woman was admitted to the San Juan City Hospital on July 18, 1950, with a history of generalized weakness, ankle edema, and orthopnea of one month's duration. She gave a noncontributory past medical history, except for an episode of joint pains three years prior to admission which lasted three months. She remained well after this episode until one month prior to admission, when she began to suffer of orthopnea, generalized weakness, and ankle swelling, and her husband noticed an icteric tinge to the skin. A private physician was consulted, and after the prescription of some "yellow pills" she improved for two weeks. Following this her symptoms returned and became progressively worse and diarrhea developed. She also mentioned the fact that her urine was dark in color. She was born and raised in an area endemic for schistosomiasis.

Physical examination revealed a blood pressure of 100/80 mm. of Hg; pulse rate, 82 per minute; respirations, 32 per minute, and temperature 98 F. The patient was a well-developed and well-nourished white woman 19 years of age, acutely dyspneic and with an icteric tinge on her sclerae, skin, and mucous membranes. There were a few palpable cervical lymph nodes on the left posterior lymphatic chain. The lungs were essentially negative except for a few moist rales. The heart was enlarged to the left. A loud presystolic crescendo murmur and a loud systolic murmur were heard at the apex. The liver was palpable about 3 fingerbreadths below the right costal margin and was tender to palpation. The spleen was also enlarged. There was a 2+ pitting edema of the lower extremities, and there was microdactylism in both feet.

Laboratory studies revealed RBC, 3,000,000 per cubic millimeter; hemoglobin, 65%; WBC 13,100 per cubic millimeter, with 70% neutrophils, 29% lymphocytes, and 1% eosinophils.

The electrocardiogram showed a chronic cor pulmonale pattern, with tall R wave in V_3 and prominent S wave in V_5.

Fluoroscopic examination done at the time of admission revealed enlargement of the right ventricle and a prominent pulmonary artery segment.

The patient was digitalized on admission, but in spite of all therapy she developed cyanosis, her dyspnea increased, and she died 20 hours after admission.

Comment.—This case was a 19-year-old white woman, who was admitted in heart failure of one month's duration. Her past medical history revealed that she had had joint pains which lasted one month. On physical examination she had scanty lung findings in comparison to the dyspnea and additional evidence of congestive heart failure. There were striking cardiac findings characterized by cardiomegaly and loud systolic and diastolic apical murmurs. Fluoroscopic examination revealed a prominent pulmonary artery segment and enlarged right ventricle.

The electrocardiogram showed right ventricular hypertrophy. These findings were interpreted as representing rheumatic heart disease with mitral stenosis and insufficiency. No attention was paid to the history of

exposure to schistosomiasis and the hepatosplenomegaly present. In spite of intravenous digitalization the patient died 20 hours after admission. This case illustrates once more the fact that schistosomal cor pulmonale with congestive heart failure, is usually confused with primary heart disease and that once the symptoms of failure appear the life expectancy is usually short.

CASE 4 (San Juan City Hospital).—A 35-year-old white woman was admitted to the gynecological service of the hospital on July 15, 1954, complaining of suprapubic pain of one month's duration.

She was in her usual state of health, except for a moderate intolerance to exercise which dated back to her childhood, and one month prior to admission she began to experience suprapubic pain which would last for two to three days and then would disappear spontaneously. There were no genitourinary or gastrointestinal symptoms. On July 1, 1954, bleeding per vagina started and lasted four days. On July 6, 1954, she again developed a sharp suprapubic pain which lasted several hours and tenderness in the area of the left adnexa. She also was slightly dyspneic. Because of recurring suprapubic pain, slight vaginal bleeding, and dyspnea the patient came to the hospital for admission.

The patient was born and raised in an area endemic for schistosomiasis, and when 18 years old she was told she had an enlarged liver and spleen. Because of a positive serology in 1949, she was treated with penicillin at the U. S. Public Health Unit. She denied any history of asthma but stated that since she was very young she could not play as strenuously as other children.

Physical examination on admission revealed a well-developed slightly obese white woman, acutely ill. The blood pressure was 100/70 mm. of Hg; pulse, 90 per minute; respirations, 20 per minute, and temperature, 99 F. There was paleness of the conjunctivae, and the lips had a dusky tinge. The lungs were clear to percussion and auscultation. Examination of the heart revealed dulness outside the left midclavicular line, pulmonic area, and apex. The liver was palpable 3 fingerbreadths below right costal margin; it was hard, nodular, and nontender. The spleen was felt 3 fingerbreadths below left costal margin and appeared firm to palpation. There was a palpable suprapubic mass which suggested an enlarged uterus, and there was moderate tenderness on the left lower quadrant. There was clubbing of the fingers, with slight cyanosis of the nails. Gynecological examination disclosed a large cystic mass on the left adnexa which was extremely tender to palpation. The clinical impression was pelvic inflammatory disease and congenital heart disease, probably interatrial septal defect.

Laboratory studies revealed RBC, 3,500,000 per cubic millimeter; hemoglobin, 7.8 gm. per 100 cc.; WBC, 5100 per cubic millimeter, with 72% neutrophils, 26% lymphocytes, 2% eosinophils, and 1% monocytes. The urinalysis was negative. The red blood cell sedimentation rate was 26 mm. in 24 hours. Blood cholesterol, 84.4 mg. per 100 cc.; total serum bilirubin, 2.18 mg. per 100 cc., with 0.48 mg. per 100 cc. in one minute. Blood serology was negative.

The electrocardiogram showed a right axis deviation and right ventricular hypertrophy.

There was no change in the clinical picture of the patient while under observation for five days. On the sixth hospital day the patient suddenly went into shock. A diagnosis of ruptured ectopic pregnancy was made. While being operated on she went into cardiac standstill, which was refractory to treatment.

Comment.—A 32-year-old white woman who was seen as an emergency medical consultation because of a loud systolic murmur detected while the patient was in shock due to a ruptured ectopic pregnancy. An interatrial septal defect was suspected by one consultant, while schistosomal cor pulmonale was suggested by another. The latter clinical impression was not verified in life, since she died in cardiac arrest while undergoing surgical intervention.

Two of our patients died in cardiac standstill while undergoing surgery. Case 1 was well compensated at the time of operation, and in this patient there was no evidence of congestive heart failure.

CASE 5 (Bayamón's District Hospital).—A 25-year-old white woman entered the hospital for the first time May 14, 1955, complaining of easy fatigability, orthopnea, paroxysmal nocturnal dyspnea, leg edema, and abdominal distention of three months' duration. She had been treated five weeks before with digitalis and a low-salt diet and improved slightly, but symptoms recurred shortly after she discontinued the regimen on her own initiative. There was no history of bronchopulmonary disease, joint pains, or of any cardiac abnormality prior to this admission. She was born and raised in Comerío, an area endemic for schistosomiasis, where she had been exposed since childhood while washing clothes in the river. She denied allergic diseases. The gastrointestinal, genitourinary, and gynecological surveys were essentially negative.

On physical examination the temperature was 98.2 F (36.8 C); pulse, 88; respirations, 28 per minute, and blood pressure, 110/70. She was dyspneic and slightly cyanotic and showed evidence of generalized edema. There was a slight cyanotic hue of cheeks, lips, and ear lobes. The neck vessels were engorged, and the hepatojugular reflux was positive. Examination of the lungs revealed the respiratory excursions to be equal bilaterally, and occasionally faint coarse moist rales were heard over both bases. The point of maximal intensity was 1 cm. to the left of the midclavicular line and the second pulmonic sound very loud. A loud blowing systolic murmur was heard in the mitral and pulmonic areas, transmitted to the left axilla, and a loud diastolic harsh murmur was heard in the pulmonic area. The abdomen was distended, and fluid waves and shifting dulness was present. The liver edge was felt 4 fingerbreadths below the left costal margin. There was a 3+ pitting pedal edema and mild cyanosis of fingernails.

Laboratory studies showed a negative VDRL. The erythrocyte count was 4,700,000 per cubic millimeter; hemoglobin, of 15.2 gm. per 100 cc.; leukocytes, 4600 per cubic millimeter; platelets, 183,000, and the hematocrit, 45 mm. The urine concentrated to 1.018, and there was 1+ albuminuria. The stools and rectal biopsy were positive for living ova of S. mansoni. Liver function tests revealed a prothrombin time of 20.4 seconds; thymol turbidity test, 12.3 units; cephalin flocculation, 4+; alkaline phosphatase, 42 King-Armstrong units; albumin, 3.7 gm. per 100 cc.; globulin, 3.1 gm. per 100 cc. The arm-to-lung circulation time with ether was 8 seconds, and arm-to-tongue with dehydrocholic acid (Decholin), 12 seconds.

Chest x-ray on admission showed the heart to be grossly enlarged, with aneurysmal pulmonary artery segment and right ventricular hypertrophy. There was a discrepancy between the increased hilar vasculature and the relative avascularity of the middle and lung periphery. The electrocardiogram showed right axis deviation and right ventricular hypertrophy.

Angiocardiography one month after hospitalization showed dilated superior vena cava, marked right ventricular enlargement, left ventricle normal in size, intraventricular septum deviated toward the left, aneurysmal dilatation of the pulmonary artery segment, and diminished to normal peripheral pulmonary vasculature.

The patient was given oxygen, mercurial diuretics, and a low-salt diet and was digitalized. Under this regimen she improved moderately well and was discharged on her seventh week of hospitalization.

Comment.—This is the third patient of the series in which the clinical diagnosis of cor pulmonale secondary to schistosomal pulmonary endarteritis was made. The pulmonary findings, physical and radiological, were not sufficient clinically to explain the degree of dyspnea. As far as we can tell it is the second patient with this disease to be studied with angiocardiogram. Cardiac chamber analysis and angiocardiography showed the right ventricular enlargement and normal auricle and ventricle, intraventricular septum with convexity toward the left ventricular chamber, and prominent hilar vasculature in discrepancy with the avascularity of the lung periphery.

The clinical course of this patient has differed from the rest of the patients presented because of a longer survival, the length of which is yet to be determined.

Pathophysiology

The histopathologic alterations encountered in the pulmonary vessels secondary to infestations with Manson's schistosomiasis, leading to pulmonary hypertension, cor pulmonale, and right-sided failure, have been sporadically reported in the literature, mostly as isolated case reports. Well-documented studies in the subject are infrequently encountered. Shaw and Ghareeb presented six cases with cor pulmonale and congestive failure; three were due to S. mansoni, and the rest, secondary to S. haematobium. Lopes de Faria analyzed 13 cases with pulmonary Manson's schistosomiasis, of which only eight had cardiac manifestations leading to death. The other five died of bleeding esophageal varices secondary to portal hypertension. All our cases had clinical evidence of heart disease and four died of cardiac failure.

The necropsy findings in these four cases disclosed changes in the pulmonary vascular tree of such interest as to warrant very careful and extensive histopathologic studies. The latter has enabled us to postulate what we believe is the sequence of events in the pathogenesis of pulmonary endarteritis due to S. mansoni and their role in the final causation of the syndrome of pulmonary hypertension and cor pumonale. A detailed

report of the histopathology of these alterations and our concept of pathogenesis merits a separate publication. In the present communication we will summarize the most important histopathologic and physiopathologic alterations leading to pulmonary hypertension.

The gross and microscopic changes in the pulmonary vessels and parenchyma in the four cases were so similar that individual case analysis is not indicated. In all the necropsies the heart was enlarged, usually due to hypertrophy of the right ventricle. The lungs disclosed numerous very small grayish granules scattered diffusely throughout the pulmonary parenchyma. These lesions were never over 1 mm. in diameter. Despite the young age of the patients, all of them exhibited moderately prominent atheromatosis of the main pulmonary arteries, undoubtedly the result of pulmonary hypertension.

The numerous lesions in the lungs should be classified in three different categories: (1) those produced directly by the ovum, (2) those encountered as the result of allergic manifestations to the ovum and its products, and, finally, (3) those secondary to pulmonary hypertension.

The ova are lodged in the pulmonary arterioles, producing a local reaction in the wall of the vessel. This is caused in all probability by a combination of both the direct mechanical effect of the ovum and its toxic products. The wall of the artery is destroyed by an inflammatory process characterized by a granulomatous reaction composed of chronic inflammatory cells and occasionally eosinophils. This reaction surrounds the ovum and extends towards the lumen of the vessel as well as through its wall. Finally, it totally occupies the lumen of the artery and in the process of extending through its wall pushes ahead of it the fragmented elastic lamellae of the vessel, producing a pseudoaneurysm (Fig. 1). The end-result is a dumbbell type (Fig. 2) of granuloma formed by the intra-arterial

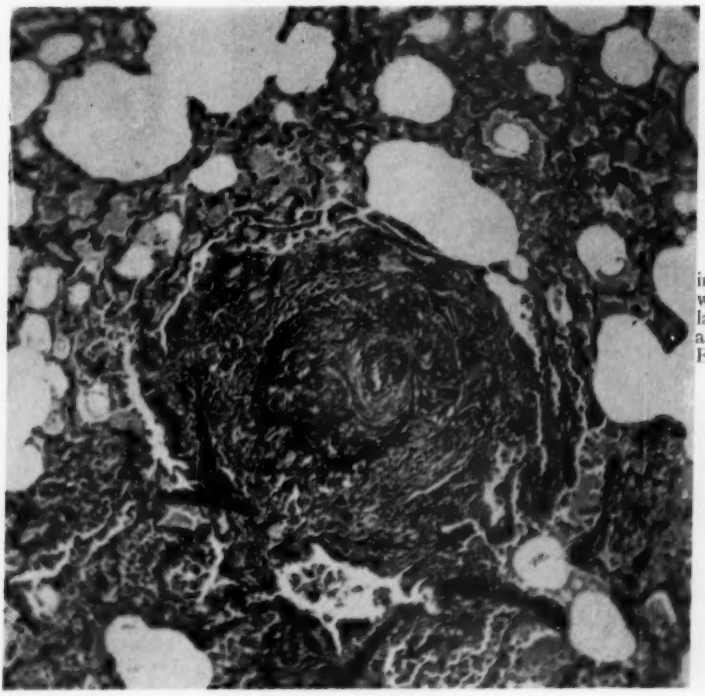

Fig. 1.—Schistosomal intra-arterial granuloma with destruction of elastic lamella and early pseudoaneurysm formation. Elastic stain; × 80.

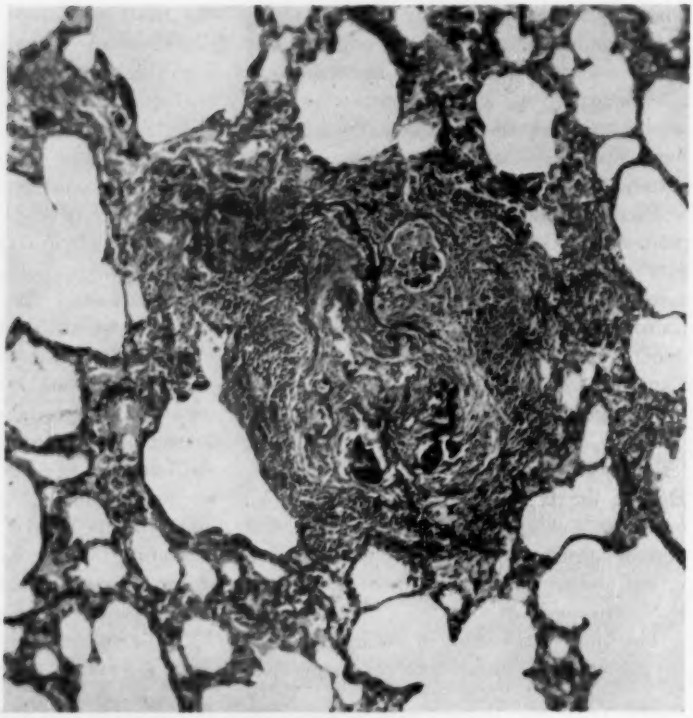

Fig. 2.—Intra-arterial and para-arterial granulomas, forming a dumbbell type of granuloma. Elastic stain; × 80.

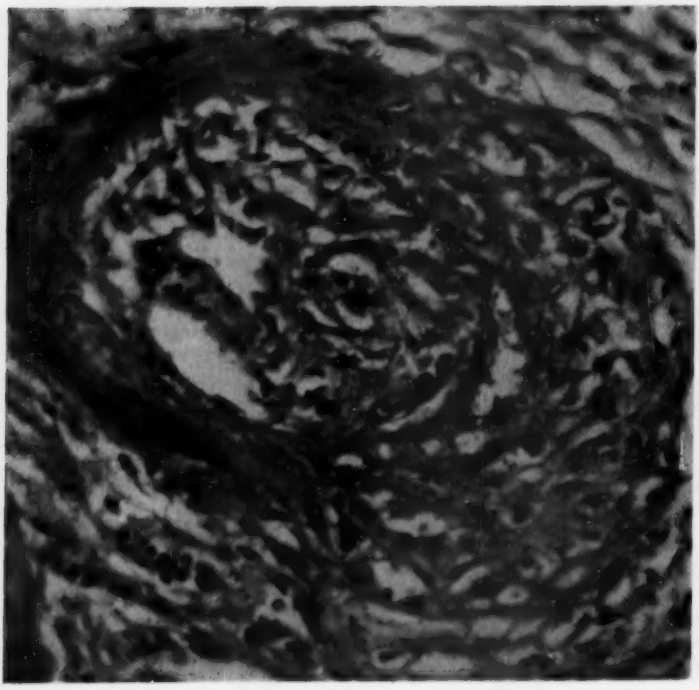

Fig. 3.—Intra-arterial angiomatoid. Hematoxylin and eosin; × 360.

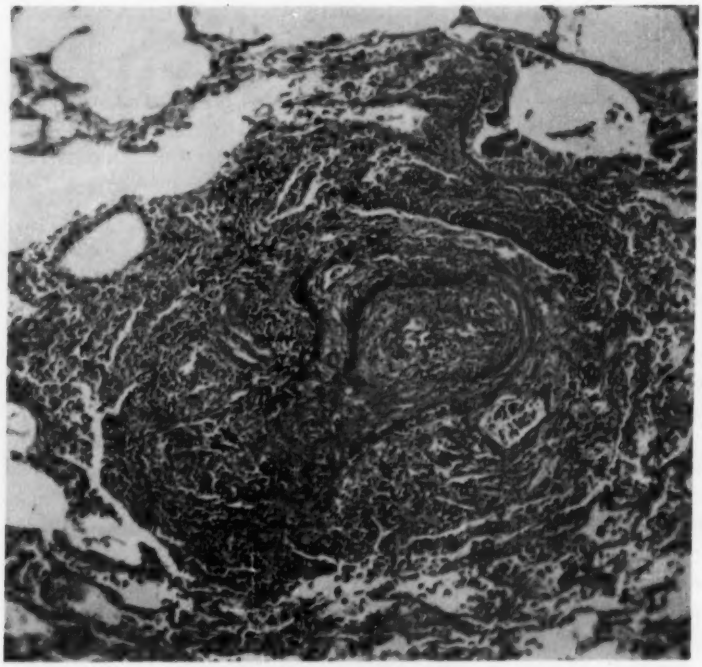

Fig. 4.—Classical paraarterial angiomatoid considered to be pathognomonic of pulmonary schistosomal endarteritis. Hematoxylin and eosin; × 80.

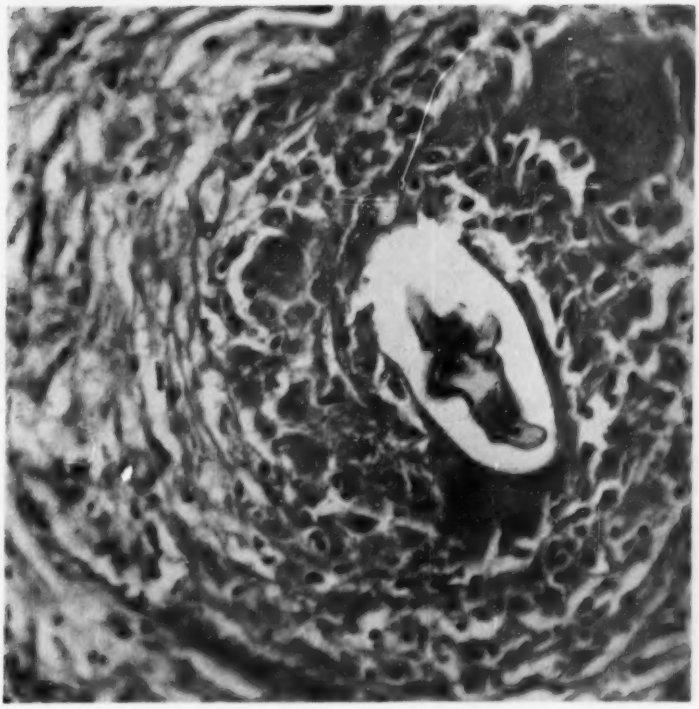

Fig. 5.—Parenchymatous interstitial schistosomal granuloma. Hematoxylin and eosin; × 360.

and the para-arterial components, joined by a granulomatous isthmus in the destroyed arterial wall. Proliferation of fibroblasts with neoformation of blood vessels occurs, in both the intra-arterial and the para-arterial granulomas. These blood vessels form communications among themselves and also with branches of the pulmonary veins destroyed by the para-arterial granuloma. We labelled the newly formed blood vessels intra-arterial angiomatoids (Fig. 3). The newly formed blood vessels in the para-arterial granuloma, which form anastomoses with the pulmonary veins and present areas of dilatation because of their arteriovenous nature, are the classical angiomatoids (Fig. 4), considered as pathognomonic of pulmonary schistosomal endarteritis.

The occlusion of the arterioles by granulomatous tissue, the pseudoaneurysms, and the arteriovenous communications play a vital role in the final production of an increased hypertension in the lesser circulation, with cor pulmonale and final right-sided failure.

It should be mentioned that occasionally an ovum goes through the wall of small arteriole, apparently producing a minimal reaction in the vessel. This ovum will produce a granuloma in the interstitial tissue. These parenchymal interstitial granulomas (Fig. 5) play no role in the causation of pulmonary hypertension.

There are other vascular changes, the cause of which can not be ascribed directly to the ovum. These lesions occur where no ova are encountered and do not exhibit the granulomatous reaction characteristic of the schistosomal pseudotubercle. We believe they are the result of an allergic mechanism. The changes are localized to the pulmonary vasculature, so the allergic phenomenon must be at a local level and not one mediated through a systemic humoral immunologic mechanism.

The two most important allergic manifestations are an arteritis and the formation of hyalin thrombi. The arteritis (Fig. 6) is characterized by fibrinoid necrosis of the wall and fragmentation of the elastic fibers.

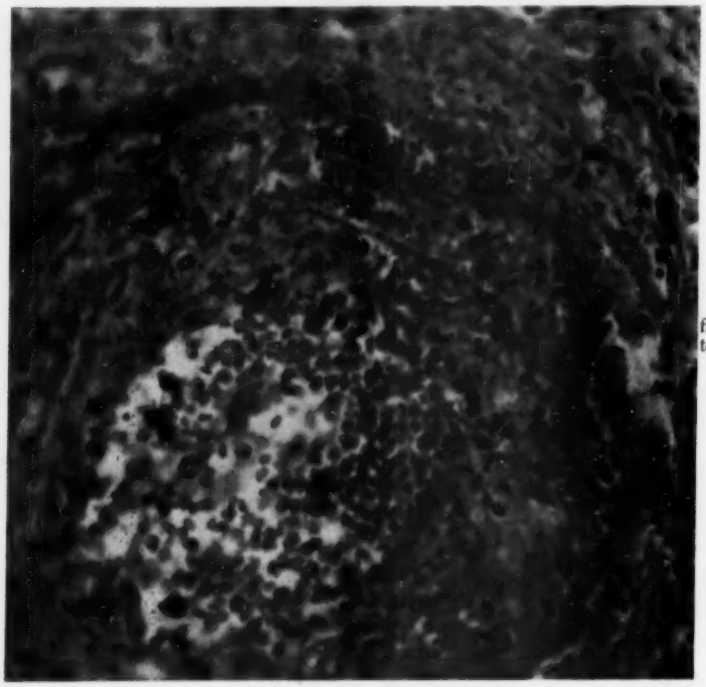

Fig. 6.—Arteritis with fibrinoid necrosis. Hematoxylin and eosin; × 360.

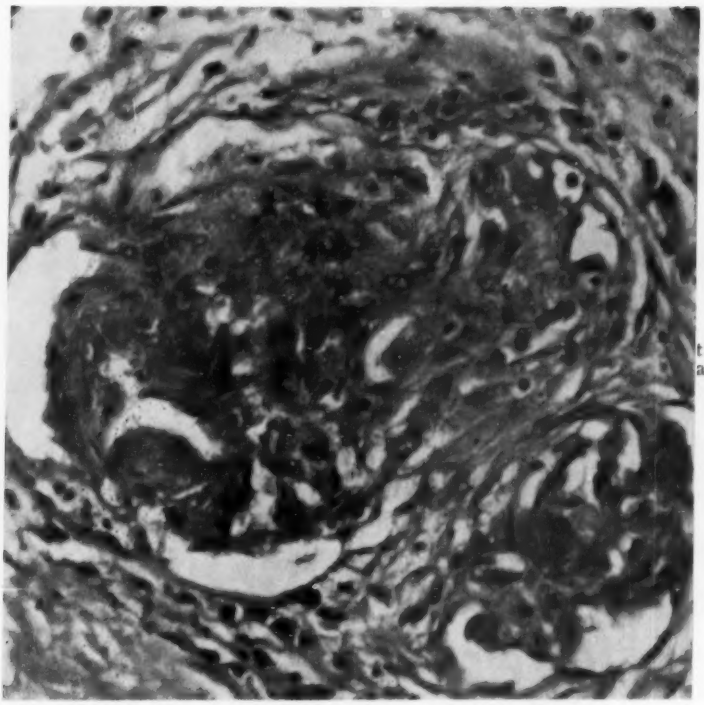

Fig. 7.—Multiple hyalin thrombi. Hematoxylin and eosin; × 360.

In places there is also an inflammatory reaction with abundant nuclear debris. These changes are strikingly similar to those of the allergic type of arteritis seen in the different disorders of collagen and nodular vasculitis.

The destruction of the media and elastic lamellae in this arteritis undoubtedly contribute markedly to the derangement of the pulmonary circulation and increased hypertension.

The hyalin thrombi are seen in many arteries (Fig. 7), arterioles, and venules as eosinophilic polypoid masses covered with endothelium. The latter forms vascular channels within the lumen of the vessel. This appears to be a process of canalization or lining of the hyalin masses by proliferating endothelium from the intima of the vessel. The physiopathologic significance of these multiple hyalin thrombi, diffusely encountered in the lungs, in the final causation of pulmonary hypertension can not be overemphasized.

The third group of vascular changes are those resulting from the increased pulmonary hypertension. These consist mostly of a diffuse fibroblastic concentric proliferation of the intima (Fig. 8), with marked reduction in the lumina of the arterioles. The media is also hypertrophied. Premature atheromatosis of the large pulmonary arteries should also be included in this third group of vascular lesions. It is needless to say how these alterations contribute to perpetuate and further increase the vascular resistance in the pulmonary circulation.

Comment

The progress achieved during the past years has in certain aspects led to a closer community of mankind. With the present means of communications the medical problems of one country concern other countries as well.

At present the public health and clinical aspects of schistosomiasis are raising some

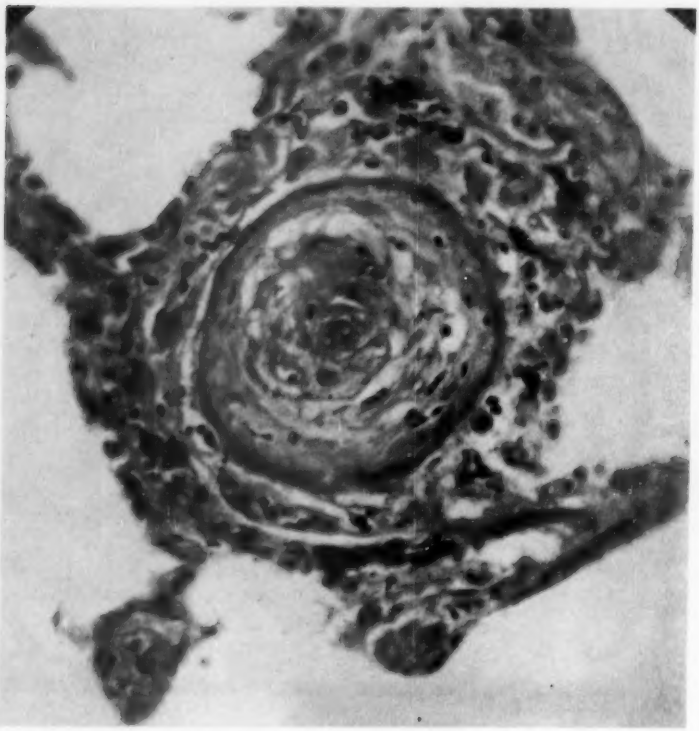

Fig. 8.—Concentric fibroblastic proliferation of the intima, with reduction in the lumen of the arteriole. Hematoxylin and eosin; × 360.

interest in the United States. This is in part due to the increasing population in the United States of people coming from areas endemic for schistosomiasis. With this worldwide interest in the disease we have presented our observations on its pulmonary aspects, chiefly that of cor pulmonale caused by S. mansoni.

The experience of physicians practicing in areas endemic for schistosomiasis is that the ravages of the disease are chiefly manifested in the younger patients but not in the elderly patients. Recurring superinfections before immunity develops seems to be an important factor. These observations have stimulated investigators to study the immunologic aspects. It has been proven beyond any doubt that exposure to Schistosoma infection leads to either partial or complete resistance to the infection.

The experiments of H. Vogel and W. Minning with periodic reinfection of Macacus rhesus, using cercaria of S. japonicum are most enlightening in this respect.[10] Particularly since the work of Oliver-González,[11] investigation of schistosomiasis now is in part being conducted by using skin and serologic tests.

The pulmonary obstruction syndrome caused by Schistosoma is seen in young adults who have lived in localities where schistosomiasis is endemic. In Egypt, contrary to what happens in Puerto Rico, men are more frequently affected than women, probably due to occupational differences.

The Table presents an analysis of the outstanding clinical findings in our small series of cases. The symptoms are usually cardiac or pulmonary. Most of the patients complained of dyspnea of short duration, usually progressive, and early manifestations of engorged neck vessels, leg edema, and painful upper abdomen. None of the cases discussed had a history of chronic bronchopulmonary disease. However, it appears that infection of the respiratory tract may be the

*Clinical and Laboratory Features of Five Cases of Schistosomal Cor Pulmonale (S. Mansoni)**

	Case 1†	Case 2	Case 3	Case 4‡	Case 5
Age	20	37	19	35	25
Sex	M	F	F	F	F
Lived in endemic area	X	X	X	X	X
Treated for schistosomiasis	0	0	0	0	0
Dyspnea	X	X	X	X	X
Orthopnea	0	Not recorded	X	0	X
P.N.D.	0	0	0	0	X
Cough	0	0	0	0	X
Cyanosis	X Lately	0	X Terminal	X	Slight X Slight
Clubbing	X Slight	0	0	X	0
Lt. chest deformity	0	0	0	0	0
Emphysema	0	0	0	0	0
Rales	0	X	X	0	0
Loud P_2	X	X	X	X	X
Systolic murmur	X	X	X	X	X
Diastolic murmur	0	X	X	0	X
Hepatosplenomegaly	X	X	X	X	X
Ascites	0	0	0	0	X
Leg edema	X	X	X	0	X
RBC, million	4.1	4.2	3.0	3.5	4.7
WBC	6,400	14,900 (infection)	13,100	5,100	4,600
Platelets	—	—	—	—	183,000
Cephalin flocculation test	3+	—	—	—	4+
Sulfobromopat halein	32%	20%	—	—	—
Stools	X	—	—	—	X
Circulation time	—	—	—	—	Normal
Venous pressure	200	Engorged neck vessels	—	—	Engorged neck vessels
ECG pattern (cor pulmonale)	X	X	X	X	X
X-ray, chest					
Rt. V. H.	X	X	X	—	X
D. P. A. S.	X	X	?	—	X
D. P. V.	X	0	?	—	X
Benefitted by digitalis	—	?	0	—	X
Time survival after onset of symptoms, mo.	8	3½	2	?	8 (still alive)

* X indicates present; 0, absent; —, not done; P.N.D., paroxysmal nocturnal dyspnea; Rt. V.H., right ventricular hypertrophy; D.P.A.S., dilated pulmonary artery segment; D.P.V., diminished peripheral vasculature.
† Died of cardiac arrest while being operated on for bleeding esophageal varices.
‡ Died of cardiac arrest while being operated on for ectopic pregnancy.

trigger factor precipitating cardiac decompensation. It is of particular interest to see these patients in respiratory distress aggravated with exertion; at times, if they are sitting quietly, dyspnea may even disappear. The picture of so much dyspnea with so few pulmonary findings is unusual. The presence of cardiomegaly with loud murmurs, usually in the pulmonic and mitral areas, suffices to suggest the diagnosis of rheumatic heart disease and congenital cardiovascular defects. That is the diagnostic challenge presented. The absence of significant pulmonary findings would suggest the absence of pulmonary parenchymal disease and the presence of hepatosplenomegaly in patients from an area endemic for schistosomiasis would be a short cut in the diagnosis. Cyanosis is rarely present, slight in degree, and usually in terminal states with cardiac failure or pulmonary sepsis. Clubbing is likewise usually absent. This appears to be because the pathological process does not affect the capillaries or alveolar septa to give the picture of alveolar capillary block of some diseases, such as Hamman-Rich syndrome.[12,13]

None of our patients had evidence of selective or total hypersplenism, and eosinophilia was usually absent. The circulation time, sometimes of crucial importance in the differential diagnosis of cor pulmonale with decompensation and primary heart disease with failure, is usually normal.

X-ray examination reveals, in posteroanterior view (Fig. 9), an enlarged right ventricle which forms the left cardiac border. This is due to the rotation of the heart. The aortic knob will appear small or absent, and the pulmonary artery segment will always be dilated, sometimes aneurysmal in size. The right hilar vasculature will be increased, while that on the left side will be inconspicuous, owing to the clockwise rotation. This radiological picture shares the pattern of mitral stenosis and congenital cardiovascular defects with dilatation of the

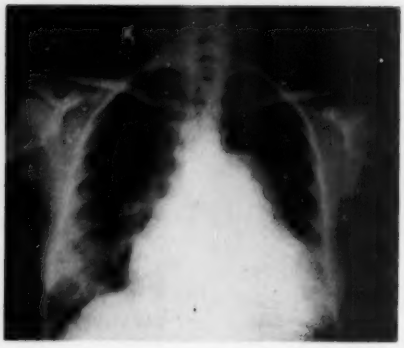

Fig. 9.—Roentgenogram showing marked dilatation of the pulmonary artery segment, right ventricular hypertrophy, and small aortic knob. The hilar vascular markings are exaggerated, while the peripheral vascular markings appear anemic.

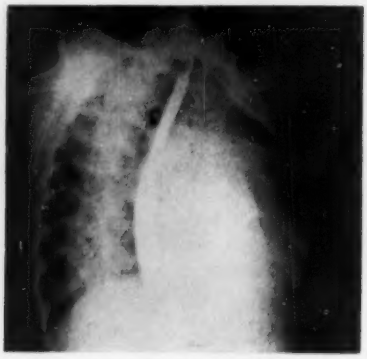

Fig. 10.—Right antero-oblique position, showing a normal left atrium.

pulmonary artery. The right antero-oblique view (Fig. 10) will show the absence of left atrial hypertrophy, and the right antero-oblique will show the left ventricle to be normal in size and sometimes a clear retrocardiac space.

Angiocardiographic studies (Figs. 11 and 12) are of a great help to confirm the x-ray and fluoroscopic findings. Abnormal cardiac and vascular communications are absent. The intraventricular septum is seen bulging toward the left ventricle (reverse Bernheim), secondary to the increase in right ventricular pressure.

The lungs may show evidence on x-ray of pulmonary schistosomiasis, characterized by fine mottling of diffuse character. Sometimes nodular infiltrations may be noted. Only one of our series showed this. The most important pulmonary finding is, however, the rather pleoanemic middle and peripheral lung fields.

The electrocardiographic pattern is shown in Figures 13 and 14. The electrocardiogram reveals a chronic cor pulmonale pattern, with a right axis deviation, marked clockwise rotation on the longitudinal axis, prominent R waves in right ventricular leads, and prominent S waves in the left ventricular leads. Inversion of the T waves, especially in Leads II_2, II_3, aV_f, and right ventricular leads, are usually noticed. These changes appear to be more marked than in other commoner varieties of chronic right ventricular strain, as in mitral stenosis. It

Fig. 11.—Angiocardiogram revealing aneurysmal dilatation of the pulmonary artery.

Fig. 12.—Left antero-oblique view, disclosing a clear retrocardiac space (R. C. S.) and the interventricular septum (I. V. S.), with its convexity bulging to the left. The dye is concentrated in the enlarged right ventricle. The left ventricle (L. V.) is normal.

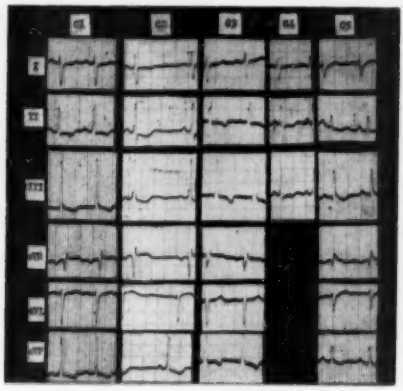

Fig. 13.—Electrocardiograms showing the limb leads of five cases of schistosomal cor pulmonale.

is of interest to note the absence of P pulmonale in most of the cases and the complexes of normal to increased voltage. It may be that cor pulmonale due to vascular, and not parenchymal, pulmonary disease is usually characterized by normal and not low amplitude complexes.

Treatment and Prognosis

The control of the trigger factor, such as pulmonary infection precipitating cardiac failure, is of paramount importance. Digitalization, oxygen administration, and other supportive measures should be administered. We should like to warn against the use of opiates and intensive antimony treatment, the latter being toxic to the myocardium.

These patients may remain asymptomatic for an indefinite period of time. Increasing knowledge of this condition and the opportunity to diagnose it clinically will enable us to better evaluate the treatment and prognosis of these patients. At present the prognosis is apparently poor once cardiac decompensation supervenes. The governing factor in the short longevity of these patients is the mechanical impairment caused by the irreversible pulmonary arterial and arteriolar obstruction. We agree with other reports that patients with a pronounced increase in pulmonary artery pressure are in a continual danger of death and hence are poor surgical risks.

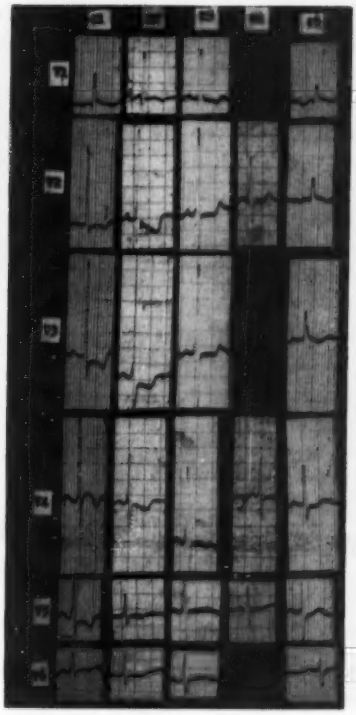

Fig. 14.—Precordial leads of five cases of schistosomal cor pulmonale.

Summary

The clinical, pathophysiological, and laboratory features of five cases of schistosomal cardiopulmonary disease caused by Manson's schistosomiasis are presented.

A young patient from an area endemic for schistosomiasis who developed dyspnea and right-sided heart failure associated with hepatosplenomegaly suggested the possibility of schistosomal cor pulmonale. The presence of an accentuated second pulmonic sound and cardiac murmurs usually cause diagnostic errors, as they may occur in congenital and rheumatic heart disease. On examination the respiratory distress is out of proportion to the scanty pulmonary findings.

The pathological lesion in the lungs responsible for the clinical picture is a widespread pulmonary obliterative arteriolitis caused by repeated ova emboli. The pulmo-

nary artery hypertension will cause right ventricular hypertrophy and eventually right-sided heart failure.

The ECG shows right axis deviation, right ventricular hypertrophy, and frequently an incomplete right bundle-branch block. Roentgenograms and angiocardiograms reveal dilated pulmonary artery segment and increased hilar and diminished peripheral pulmonary vascular markings, with a prominent right ventricle.

The differentiation of pulmonary obstruction syndrome due to schistosomiasis from cor pulmonale due to pulmonary parenchymal disease and primary heart disease with failure is of paramount importance. Further observations will enable us to learn more about the natural course and prognosis of this disease. However, it appears the longevity is short once cardiac decompensation ensues.

Dr. Carlos Guzmán Acosta and Dr. Rafael Díaz Bonnet helped in the x-ray studies, and Mrs. Gladys L. Anglada assisted in preparation of the manuscript.

Box 6671, Loiza St. Station, Santurce, P. R.

Addendum

Since submitting this paper for publication, five additional patients with schistosomal cor pulmonale have been seen and are under careful study and observation. The findings in these cases are similar to the ones presented in this communication.

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Hirsutism

WILLIAM H. PERLOFF, M.D.; HARRY E. HADD, M.A.; BERTRAM J. CHANNICK, M.D., and JOHN H. NODINE, M.D., Philadelphia

To the unfortunate woman afflicted with hirsutism, excessive facial and/or body hair represents a serious aesthetic and psychological problem; to her physician, it often presents a frustrating dilemma in diagnosis and management. Usually benign, it may be the sole manifestation of a serious underlying endocrine disorder. Hirsutism has been noted in children with hypothalamic lesions,[1] congenital ectodermal dysplasia,[2] hypothyroidism,[3] polyostotic fibrous dysplasia,[4] inanition and wasting, and under body casts worn for long periods of time. The starvation state, also called "the hibernation syndrome," is also associated with hirsutism in adult females; the reason for excessive hair growth is unknown. Pituitary gland tumors are found occasionally in women with signs of virilization including hirsutism; in most instances manifest adrenocortical hyperplasia is present, suggesting mediation through the adrenals.

Hyperplasia or tumor of the adrenal cortex leads to one or a variable combination of two syndromes. If the abnormality involves only hydrocortisone metabolic pathways, Cushing's syndrome results, and findings include mild hirsutism, insulin-resistant diabetes, rounding of the face, hypertension, osteoporosis of the spine, and elevated urinary 11-oxysteroids. When testosterone-like hormones are produced in excess the adrenogenital syndrome ensues, the exact clinical picture depending on the time of onset. Typically, it includes virilization with marked hirsutism, enlargement of the clitoris, deepening of the voice, balding of the head, amenorrhea, and elevated urinary neutral 17-ketosteroids. Adrenal tumors usually produce higher levels of urinary 11-oxysteroids and/or 17-ketosteroids than does hyperplasia. Differentiation is also facilitated in the adrenogenital syndrome by the capacity of cortisone or prednisone to lower excretion of urinary 17-ketosteroids in patients with hyperplasia.

Pathologic states or tumors of the ovaries, adrenal rests, Leydig-cell tumors, teratomata, and arrhenoblastoma are implicated in the pathogenesis of hirsutism. Diffuse luteinization (hyperthecosis)[5] and polycystic ovaries of the Stein-Leventhal type[6] are also etiologic possibilities. In these two conditions virilization is unusual, but menstrual disorders, including amenorrhea, are common. Total neutral urinary 17-ketosteroids are normal or slightly to moderately elevated, and diagnosis often depends on surgical exploration and histologic examination of ovarian sections.

Hirsutism has been reported in patients with thymic tumors,[7] metabolic craniopathies (Stewart-Morgagni-Morel syndrome),[8] during menopause, and during pregnancy[9]; the mechanism is not understood. And, finally, there are likely certain women with congenitally sensitive hair follicles in whom normal concentrations of serum androgens result in profuse hair growth. It is obvious that most patients require careful study, including an extensive endocrine survey, before a diagnosis can be established. When

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From the Department of Endocrinology, Temple University School of Medicine and Medical Center. Associate Professor of Medicine and Director of the Department of Endocrinology (Dr. Perloff); Instructor in Endocrinology and Endocrine Chemist (Mr. Hadd), and Instructors in Medicine (Drs. Channick and Nodine).

a functioning tumor of the ovary or adrenal gland is discovered, removal results in a therapeutic triumph. More commonly, no definite etiology is found, and the diagnosis of "idiopathic hirsutism" is made. This type of hirsutism is often familial, occurring in women whose ancestors stem from the Mediterranean area, which adds to the impression that it is "normal" for certain ethnic groups.

Early investigators reported urinary androgen and total neutral 17-ketosteroid levels as normal, slightly elevated, or even low.[10-13] Employing newer techniques of chemical analysis which permit division of total 17-ketosteroids into constituent components, recent workers have indicated that idiopathic hirsutism is due to selective adrenocortical hyperfunction with disproportionate increase in the production of certain hormones.[13-15] We have been able to confirm these findings and have apparently relieved both the metabolic abnormalities and the hirsutism with small doses of prednisone.*

Methods

Total neutral 17-ketosteroids in urine were measured by a modification of the Zimmerman technique after acid hydrolysis. A second aliquot of urine was hydrolyzed with β-glucuronidase, extracted with chloroform, and chromatographed on paper strips in a toluene/propylene glycol (methanol diluted) system[16] to separate the 11-oxygenated metabolites ($C_{19}O_3$) from the 11-desoxy derivatives ($C_{19}O_2$). The $C_{19}O_3$ 17-ketosteroids (11-β-hydroxyandrosterone, 11-ketoandrosterone, 11-β-hydroxyetiocholanolone and 11-ketoetiocholanolone) represent metabolic end-products of hydrocortisone and related weakly androgenic hormones, whereas $C_{19}O_2$ 17-ketosteroids (androsterone, etiocholanolone, and dehydroepiandrosterone) result from the metabolism of more strongly androgenic precursors.

Five women with the Stein-Leventhal syndrome and sixteen patients in whom this and other causes of hirsutism had been eliminated were studied as above, photographed, and given 7.5-15 mg. of prednisone a day. At approximately monthly intervals urine tests were repeated, the daily dose of prednisone adjusted, and excess hair removed with a wax depilatory. In some instances serial specimens of wax containing hair were photographed.

Results

Urinary hormone levels and daily doses of prednisone are listed in the Tables. Formerly, we considered the normal daily range of total neutral 17-ketosteroids in women to be 6 to 15 mg., at times as high as 18 to 20 mg. We now question this interpretation of the higher values. It is apparent from Tables 1 and 3 that levels of urinary total neutral 17-ketosteroids and $C_{19}O_3$ fractions are not necessarily helpful diagnostically, since they often fall within the normal range

TABLE 1.—*The Effect of Prednisone on the Urinary Total Neutral 17-Ketosteroids of Hirsute Women*

Patient	Diagnosis	(Zimmerman), 17-Ketosteroids Mg./24 Hr.	Prednisone (4 wk.), Mg./Day	(Zimmerman) 17-Ketosteroids Mg./24 Hr.	No Therapy, Mo.	(Zimmerman), 17-Ketosteroids Mg./24 Hr.
C.P.	Stein-Leventhal	28.1	10	11.1		
A.P.	Stein-Leventhal	27.0	15	10.0		
F.O.	Stein-Leventhal	18.1	10	9.5		
B.R.	Hirsutism	21.3	10	9.9		
E.D.	Hirsutism	17.0	10	6.3		
			7.5	9.7		
L.S.	Hirsutism	17.0	15	6.6	3	13.5
S.W.	Hirsutism	14.0	10	6.3	8	9.8
S.P.	Hirsutism	13.7	10	7.0		
			15	3.6	8	11.0

TABLE 2.—*Urinary 17-Ketosteroids in Normal Controls*

Patient	Sex	17-Ketosteroids, Mg./24 Hr.			
		Zimmerman Test	$C_{19}O_2$	$C_{19}O_3$	Total
N. McC.	F	13.3	4.7	2.5	7.2
B. S.	F	10.3	4.4	3.6	8.0
B. P.	F	6.2	2.8	2.8	5.6
S. W.	F	10.5	4.7	2.7	7.4
G. G.	M	13.1	5.5	3.8	9.3
J. McG.	M	16.3	6.9	6.6	13.5

* The Schering Corporation provided the prednisone (Meticorten) used in this study.

despite the presence of hirsutism. Of more significance are the pretreatment levels of $C_{19}O_2$ 17-ketosteroid fractions (Table 3), which are uniformly elevated in these patients—5.8-14.9 mg. (normal under 5 mg.? Table 2). High values fell with therapy in proportion to the dose of hormone employed, so that we were able to maintain levels of 7.4 mg. or less in all patients with daily doses of 7.5 to 15 mg. of prednisone. We believe it desirable to keep the total level at 8 mg. per day and the $C_{19}O_2$ fraction under 5 mg. per day.

Clinical results also were gratifying. Excess hair regrew at successively slower rates in all patients, becoming sparser and finer with each wax depilation. Within three to eight months further hair removal often was unnecessary. Eleven patients had excellent results; seven women thought the clinical results were good; two rated the treatment as fair, and one patient thought

TABLE 3.—*17-Ketosteroid Fractions in Hirsute Women*

Patient	Diagnosis	17-Ketosteroids, Mg./24 Hr.				Prednisone (4 wk.), Mg./Day	17-Ketosteroids, Mg./24 Hr.			
		Zimmerman Test	$C_{19}O_2$	$C_{18}O_2$	Total		Zimmerman Test	$C_{19}O_2$	$C_{18}O_2$	Total
D. S.	Stein-Leventhal	16.0	12.6	3.3	15.9	10	10.5	7.0	2.9	9.9
R. V.	Stein-Leventhal	15.1	7.1	3.9	11.0	10	5.9	5.2	1.8	7.1
R. C.	Hirsutism	25.7	14.1	6.9	21.0	10	14.1	7.4	5.5	12.9
L. D.	Hirsutism	22.7	12.2	2.9	15.1	10	12.7	7.5	3.5	11.0
						0*	12.7			
V. G.	Hirsutism	22.2	8.3	4.1	12.4	15	8.9	5.7	3.2	8.9
P. A.	Hirsutism	20.5	13.9	4.3	18.2	10	7.7	7.3	3.3	10.6
						10	4.0			
M. R.	Hirsutism	18.5	8.4	4.2	12.6	15	3.0			
D. L.	Hirsutism	18.1	14.9	3.2	18.1	10	9.0			
U. B.	Hirsutism	16.7				10	7.4	1.2	0.8	2.0
						15	5.8	0.9	0.9	1.8
E. B.	Hirsutism	14.5	6.5	4.0	10.5	10	4.1	3.7	2.2	5.9
R. G.	Hirsutism	12.0	7.6	1.4	9.0	10	6.1	4.8	1.0	5.8
J. Z.	Hirsutism	9.1	7.0	1.9	8.9	10	5.8	4.8	1.4	6.2
A. K.	Hirsutism	8.2	5.8	3.9	9.7	10	6.2	3.9	2.9	6.8

* 3 mo. after cessation of therapy; treated 6 mo., 10 mg./day.

Figure 1

Figure 2

the improvement in hirsutism was not worth the expense and trouble. The effect of treatment on menstrual function and fertility will be the subject of a separate report. In two patients total 17-ketosteroids were within the normal range when last measured, eight months after cessation of therapy. No serious undesirable side-effects were noted, although approximately one-half of all patients complained of transient fatigue of one to two months' duration. Photographs of two patients taken before and after treatment are shown in Figures 1 and 2.

The exact nature of this disorder is not clear, but intimate adrenocortical involvement appears certain from our results and those of others,[13,14] particularly Kappas et al.,[15] who call it, " 'a transitional' syndrome, removed from normal, but different in degree and kind from the adrenogenital syndrome. . . ." One might postulate the following sequence of events: 1. increase in corticoid requirements, as at puberty; 2. relative insufficiency of hydrocortisone production owing to a deficiency of chemical precursors or adrenal enzymatic defects; 3. inadequate level of blood corticoids; 4. pituitary gland release with production of larger than normal amounts of adrenocorticotropic hormone (ACTH); 5. increased stimulation of adrenocortical function until hydrocortisone production becomes adequate, but, simultaneously, 6. excessive synthesis of androgen, resulting in the urinary hormonal pattern found in our patients, i. e., normal levels of corticoids and their derivatives, and elevated androgens and their metabolic end-products. Unexplained is the reason for the maintainance of normal 17-ketosteroid values eight months after suppressive therapy was discontinued.

Summary and Conclusions

Urinary levels of total neutral 17-ketosteroids as well as $C_{19}O_2$ (strong androgens) and $C_{19}O_3$ (weak androgens) fractions were measured in patients with "idiopathic hirsutism" and control subjects. Total 17-ketosteroids and $C_{19}O_3$ fractions were

generally higher in patients with hirsutism, but there was considerable overlapping with normals. The $C_{19}O_2$ 17-ketosteroid fraction was uniformly elevated, and daily doses of 7.5-15 mg. of prednisone reduced these levels to normal or almost normal. Reduction in the amount, rate of growth, and coarseness of superfluous hair followed prednisone administration, particularly when wax depilation was performed concurrently. Improvement in both the hormonal excretory pattern and hirsutism persisted for at least eight months after cessation of therapy. No important side-effects occurred, but one-half of all patients complained of transient fatigue. On the basis of this and other studies we believe that despite the prevalence of idiopathic hirsutism and its familial distribution, it represents a type of adrenocortical hyperfunction which is abnormal, undesirable, and remediable.

3521 Broad St. (40).

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Case Reports

Vitamin K Deficiency Associated with Prolonged Antibiotic Administration

HALCOTT T. HADEN, M.D., Atlanta

Vitamin K deficiency as the cause of a hemorrhagic diathesis has been recognized for many years. Clinical deficiency of this vitamin has usually been associated with some defect in absorption from the gastrointestinal tract, such as that associated with biliary-tract obstruction or with sprue. Dietary deficiency of vitamin K has not been important because of the ability of the normal intestinal bacteria to synthesize vitamin K. Since the introduction of the broad-spectrum antibiotics it has become possible to greatly reduce the bacterial content of the intestine and, as a consequence, to decrease the amount of vitamin K produced. The fact that this can occasionally produce a severe hemorrhagic diathesis is attested by the following case.

Report of Case

A 46-year-old white woman was admitted to the urology service of the Medical College of Virginia Hospital on June 6, 1956, because of right ureteral obstruction and chronic renal infection. Five years previously she had had a calculus removed from the left kidney. She had developed chronic infection in the left kidney two years previously, and, since the left kidney was found to be nonfunctioning, it was removed. Subsequently she had developed renal calculi on the right, necessitating ureterolithotomy in March, 1955, and again in September, 1955. After this she had developed partial obstruction of the right ureter, with right hydronephrosis and repeated renal infection.

She had been hospitalized for six months at another hospital prior to admission, and two explorations of the right ureter were performed during that time in an attempt to reestablish adequate ureteral drainage. This had not been successful, and the urine was drained through a right nephrostomy. She had eaten poorly during this time and had had repeated bouts of renal infection. Because of the persistent renal infection she had received long courses of various broad-spectrum antibiotics orally.

Examination on admission revealed a pale thin chronically ill middle-aged white woman. The tongue appeared quite red, and there was slight cracking at the corners of the mouth. The remainder of the physical examination was negative except for the scars of her previous operations.

Laboratory studies on admission revealed a hemoglobin value of 10 gm. per 100 cc. and a white blood cell count of 6350. The urine had a specific gravity of 1.009 and contained 1+ albumin and many white blood cells. Blood urea nitrogen was 25 mg. per 100 cc.; serum calcium, 9.6 mg. per 100 cc.; serum phosphorus, 4.0 mg. per 100 cc.; serum alkaline phosphatase, 2.4 Bessey-Lowry units (normal 0.8-2.9 units); urine Sulkowitch test, negative. Serum protein was 5.4 gm. per 100 cc., with 2.9 gm. albumin and 2.5 gm. globulin. Serum bilirubin was 0.2 mg. per 100 cc. total and 0.05 mg. per 100 cc. direct-reacting. Thymol turbidity was negative. A urine culture grew Aerobacter aerogenes, sensitive in vitro to chloramphenicol (Chloromycetin) and to nitrofurantoin (Furadantin). Chest x-ray was normal. Intravenous and retrograde pyelograms revealed a stenosis of the middle one-third of the right ureter and a hydronephrosis on the right.

Because of the stenosis of the right ureter, it was felt that the patient should have a ureter constructed from an isolated section of ileum. In preparation for this procedure, she was given 3 gm. of neomycin orally for three doses. On June 15 the patient underwent a right ureteroileocystostomy without difficulty. Postoperatively she received parenteral fluids, antibiotics, and vitamin supplements. Five days postoperatively the patient began to take oral feedings and was switched to oral tetracycline and multivitamin supplements. One week after operation the patient developed fever and purulent urine began to drain from the

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nephrostomy tube. On the 10th postoperative day tetracycline was stopped, and she was given oral chloramphenicol and sulfisoxazole (Gantrisin).

On July 2, seventeen days after operation, the patient passed a large amount of red blood by rectum. After this she continued to pass small amounts of blood by rectum, began to cough up blood-streaked sputum, and developed oozing of blood from sites of previous venipunctures and hypodermoclyses. Coagulation studies done at that time were as follows: bleeding time at ear lobe, over one hour; clotting time (Lee-White), 50 minutes; prothrombin time, 58 seconds (control, 14 seconds); prothrombin concentration, 6%; prothrombin consumption, 50%; fibrinogen, 543 mg. per 100 cc.; platelet count, 157,000. Factor VII was 5%, and Factor V was 85%. The actual prothrombin concentration as determined by the two-state prothrombin time was 42 units, or 17.5%. BUN at that time was 28 mg. per 100 cc., and the hematocrit reading was 24%.

The patient was treated with 100 mg. of phytonadione (vitamin K_1 [Mephyton]) intravenously and received 500 cc. of fresh whole blood. Six hours later she was still bleeding from various sites, and she was given another 100 mg. of phytonadione intravenously in 500 cc. of 5% dextrose in water. She also received a second transfusion of 500 cc. of fresh whole blood. The patient continued to show evidence of bleeding during the evening of July 2, with recurrent bloody stools and persistent oozing from the site of a hypodermoclysis in the right thigh. The bleeding subsided during the night, and on the morning of July 3 there was no evidence of further bleeding. Repeat prothrombin time on July 3, twenty hours after the initial injection of phytonadione, was 100%. Parenteral phytonadione was continued for several days, and on July 6, four days after the onset of bleeding, the prothrombin concentration was 80% and Factor VII was 100%.

The patient had no further evidence of bleeding during this hospitalization and subsequently underwent a pyeloileostomy without difficulty. She was discharged on Sept. 16, 1956, and has remained well since.

Comment

The occurrence of a hemorrhagic diathesis due to a deficiency of vitamin K has been recognized since around 1935.[1] It was soon found that vitamin K is synthesized by bacteria, and Almquist, Pentler, and Mecchi[2] found that cultures of Staphylococcus aureas, Escherichia Coli, Bacillus subtilis, Sarcina lutea, and Mycobacterium tuberculosis all contained abundant vitamin K. Many attempts to produce a hemorrhagic disease in mammals by feeding a diet deficient in vitamin K have failed. Apparently there is absorption of sufficient vitamin K synthesized in the intestine by bacteria, to prevent the development of a deficiency. Vitamin K is found in a wide variety of foods, with the largest amounts being found in green leafy vegetables.

Vitamin K deficiency has been noted in association with a wide variety of intestinal diseases. Among these are obstructive jaundice, biliary fistula, sprue, chronic diarrhea, and chronic ulcerative colitis. Hypoprothrombinemia may, of course, be associated with other states, such as liver disease and ingestion of coumarin derivatives.

In the case reported there was no diarrhea or other apparent disturbance in intestinal function. Stools were normal in appearance. There was no evidence of liver disease, and the prothrombin time returned to normal promptly after the administration of vitamin K. No coumarin derivatives had been given. The patient's diet had been deficient owing to the anorexia associated with her chronic illness, but we cannot say how deficient it was in vitamin K. Supplements of other vitamins had been given intermittently. The prolonged oral antibiotic therapy had undoubtedly reduced the intestinal bacterial flora to a minimum, with consequent loss of vitamin production in the intestines. The combination of deficient diet plus loss of bacterial synthesis of vitamin K produced a deficiency of vitamin K and resulted in a hemorrhagic diathesis.

The fact that this patient did not bleed until after her operation is not surprising. It was well recognized before the general use of vitamin K therapy that the bleeding tendency in obstructive jaundice was often observed several days postoperatively. Although there would be no evidence of excessive bleeding at operation, massive and fatal hemorrhage might occur a few days after operation. Butt, Snell, and Osterberg[3] described a group of patients with prolonged plasma prothrombin time and

postoperative hemorrhage. The bleeding occurred usually between the first and fourth postoperative days, but occasionally hemorrhage was not observed until later, on the 18th day after operation in one case.

In recent years the importance of Factor VII (proconvertin, stable factor, serum prothrombin conversion accelerator) in the clotting mechanism has been elucidated. The presence of this factor is essential for the normal conversion of prothrombin to thrombin. It is decreased by the usual prothrombinopenic agents (bishydroxycoumarin [Dicumarol], ethyl biscoumacetate [Tromexan Ethyl Acetate], phenindione), and rare cases of an isolated congenital deficiency have been reported. Vitamin K is necessary for its formation. As in the case presented, it is decreased in vitamin K deficiency and, in the presence of good liver function, responds promptly to vitamin K administration. It has recently been reported by Lewis et al.[4] that PTC (plasma thromboplastin component) is also decreased in vitamin K deficiency, along with prothrombin and Factor VII. PTC was not measured in this case.

Summary

A case of vitamin K deficiency associated with deficient diet and prolonged oral broad-spectrum antibiotic therapy is presented. Bleeding occurred 17 days after operation. Laboratory studies showed a low level of prothrombin and Factor VII. There was a rapid response to parenteral vitamin K administration.

Lowance Clinic, 46 Fifth St., N. E.

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Atrial Flutter with 1:1 A-V Conduction

JACK MARKS, M.D., Columbus, Ohio

Atrial flutter usually occurs with some degree of A-V block; however, uncommonly it occurs without A-V block, i. e., with 1:1 A-V conduction. This is an infrequent arrhythmia and is regarded as the most rapid form of tachycardia known to occur in the adult.[2] It is a prostrating event because of the extreme rapidity of the heart beat. Ventricular rates up to 320 beats per minute have been reported.[2] In at least two instances death has occurred following such paroxysms.[3,26] Although this disorder occurs infrequently, as judged by the paucity of its report in the literature,[26] it has the potentiality of occurring more frequently through the use of cardiodepressant drugs, such as quinidine.

In 1915 Lewis published the first electrocardiographic tracing of atrial flutter with 1:1 A-V conduction of a patient with a ventricular rate of 270 beats per minute.[1] Approximately 46 additional cases have been published.[26] The following is a report of another instance of this disorder.

A 37-year-old white man was admitted to the South Unit of the Youngstown Hospital Association, Youngstown, Ohio, on Feb. 12, 1955, with complaints of shortness of breath and rapid heart beating of several months' duration. On admission pulse rate was 140 beats per minute and B. P. was 196/130. An ECG taken two days after admission showed atrial flutter with 2:1 and 3:1 A-V block. Protein-bound iodine determinations of 8.9γ and 9.7γ per 100 cc. were obtained. I^{131} uptake was normal. The patient was treated with digitalis, which effected a change in rhythm to atrial fibrillation; with the administration of quinidine sulfate it converted to regular sinus rhythm. He was discharged from the hospital on March 13, 1955. Discharge medication consisted of quinidine sulfate, 0.2 gm. t. i. d., phenobarbital, and belladonna tincture.

On March 26 the patient returned to the hospital again in atrial flutter with 2:1 A-V block. The ventricular rate was 145 beats per minute. He was treated with progressively increasing doses of quinidine, and on March 30 an ECG showed atrial flutter with 2:1 A-V block, with an atrial rate of 260 and a ventricular rate of 130 beats per minute (Fig. 1). On March 31, at noon, the patient suddenly developed atrial flutter with 1:1 A-V conduction with a ventricular rate of 260 beats per minute (Fig. 2). He was given 0.8 mg. of lanatoside C and 16 mg. of morphine sulfate intravenously. Atrial flutter with 2:1 A-V block was thereby restored (Fig. 3).

In 1933 Bedell[8] reviewed 21 cases of atrial flutter with 1:1 A-V conduction and reported three additional cases. She divides these cases into three groups. The two cases in the first group were characterized by gradually increasing ventricular rates to 240 and 273 beats per minute, respectively, upon which abnormal QRS complexes developed, and there followed in each instance 2:1 A-V block. The second group of cases, number-

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Senior Assistant Resident, Department of Medicine, The Ohio State University Health Center.

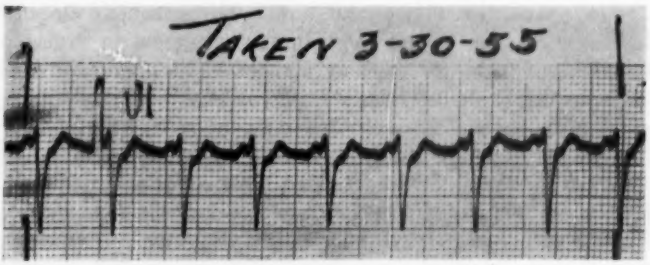

Fig. 1.—Atrial flutter with atrial rate of 260 and ventricular rate of 130 beats per minute.

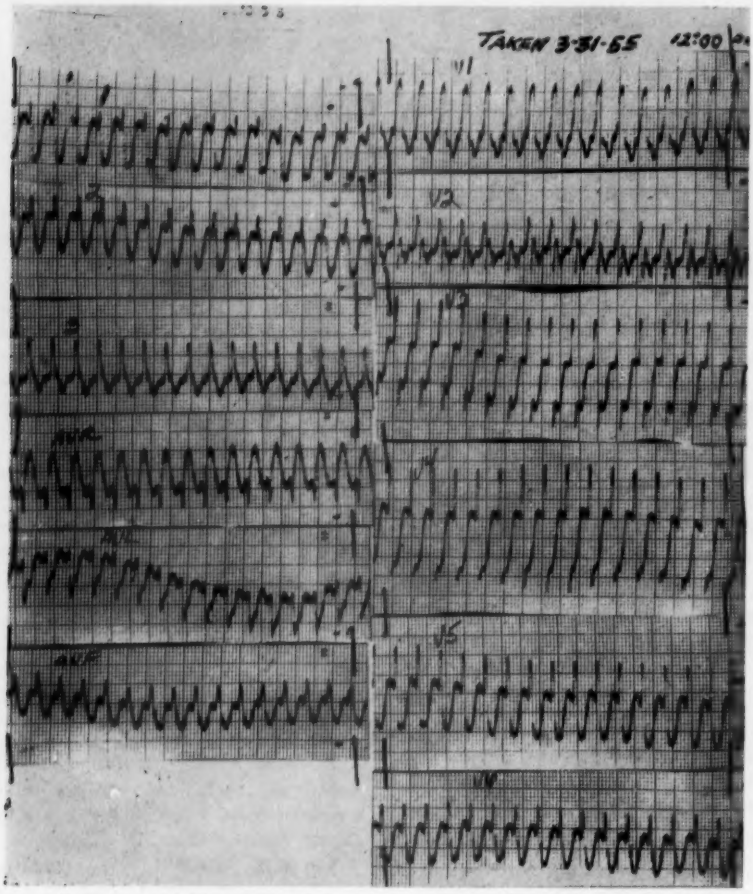

Fig. 2.—Atrial flutter with 1:1 A-V conduction. Rate, 260 per minute.

ing four instances, was likened to "auricular tachysystole of childhood." It was noted that this disorder seemed to differ from paroxysmal atrial tachycardia only in that the ventricular response exceeded the maximum rate ascribed to paroxysmal atrial tachycardia, given variously at 200 to 220 beats per minute. No A-V block was observed in these cases. Bedell stated that these cases should probably be classed with paroxysmal atrial tachycardia, to which they were more closely related than to atrial flutter with 1 : 1 A-V conduction. The third of Bedell's groups comprised a large unified group of 18 cases in which atrial flutter with A-V block was clearly adduced before and/or after the paroxysms of 1 : 1 flutter. Finkelstein et al.[26] have considered this a criterion for diagnosis of the disorder.

Comment

No single variety of heart disease has been associated predominantly with atrial flutter with 1 : 1 A-V conduction. Bedell[8] listed no heart disease present in 9 of the 24 cases reviewed. Atrial premature contractions were listed as the only manifestations of underlying heart disease in three additional cases of this group. White and Stevens[5] reported the cessation of attacks of 1 : 1 flutter in a 38-year-old woman after the excision of cervical ribs. Thyrotoxic,

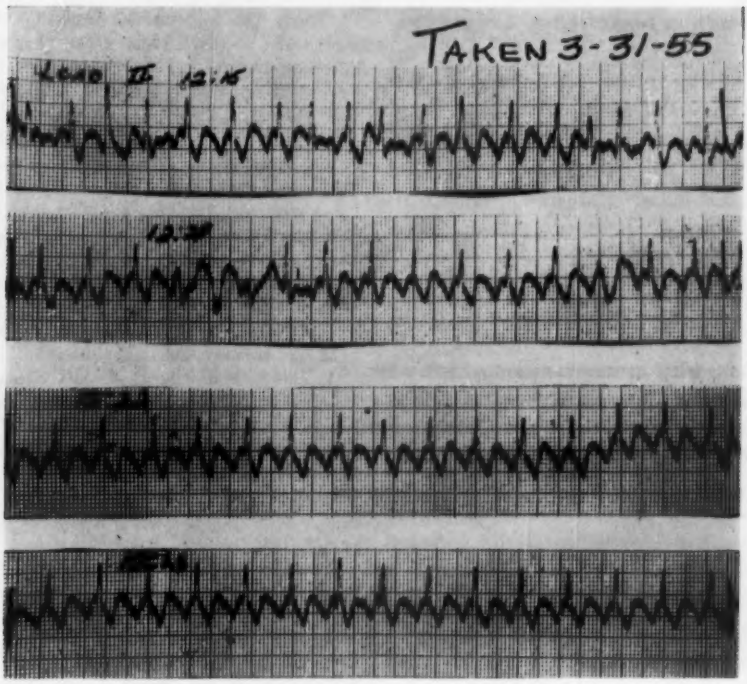

Fig. 3.—Atrial flutter, 2:1 A-V block.

rheumatic, arteriosclerotic, and syphilitic heart disease have been present in patients who experienced this disorder.[3]

An autopsied case recently reported by Finkelstein et al.[26] was that of a 16-year-old Negro girl who died three days after the cessation of a protracted bout of atrial flutter with 1:1 A-V conduction. No anatomic cause of death could be assigned from the necropsy findings.

Atrial flutter with 1:1 A-V conduction has in many of the reported cases been a consequence of the administration of quinidine to patients having atrial flutter with 2:1 A-V block.[19,22,24] The mechanism appears to be one of quinidine slowing the atrial rate to a point where the conductive tissues become responsive to each atrial impulse instead of to every other atrial impulse. Lewis [9] showed that the A-V node of the cat was capable of responding to individual stimuli up to a frequency of 300 impulses per minute, but above this rate every other impulse was conducted. Quinidine through its vagolytic effect [36] also tends to decrease the refractive period of the nodal tissue, thereby enhancing the transmission of frequent atrial impulses through to the ventricular musculature. Contrariwise, digitalis tends to decrease the refractive period of the atrial tissues and to increase the refractive period of the conductive tissues, thereby tending to change atrial flutter into fibrillation and to permit fewer atrial impulses to reach the bundle of His.[36] Bellet [16] has stated that digitalis will interrupt atrial flutter in 70% of cases with the production of atrial fibrillation and on cessation of digitalis therapy the rhythm reverts to sinus rhythm in two-thirds of this number. In those persons with atrial fibrillation whose rhythm does not revert to sinus rhythm on discontinuation of digitalis quinidine should then be administered.[29] In those instances of atrial flutter where toxic doses of digitalis fail to terminate the flutter mechanism quinidine should be given under close supervision, with cognizance of the

hazard of such an undertaking. If quinidine be truly vagolytic then the prior and concomitant administration of digitalis to the patient with atrial flutter and A-V block would not insure the prevention of atrial flutter with a 1:1 response.

As in atrial flutter with slower ventricular rates of response the treatment of choice of atrial flutter with 1:1 A-V conduction is digitalis.[2,3,12,13,19,26] Smelin et al.[18] have reported the successful termination of an instance of atrial flutter with 1:1 A-V conduction with intravenously administered phenylephrine (Neo-Synephrine). While it seems contraindicated to tax further the maximally stressed heart in 1:1 flutter with a sympathomimetic agent, still, where other measures repeatedly fail, it would seem that phenylephrine warrants a therapeutic trial.

While atrial flutter with 1:1 A-V conduction appears to be an uncommon cardiac arrhythmia, it represents a catastrophic event that requires prompt therapy.

Summary

Approximately 47 cases of atrial flutter with 1:1 A-V conduction have been reported.[26] An additional case is presented. The hazard of quinidine therapy in the presence of atrial flutter with 2:1 A-V block is discussed.

This case is reported by permission of Dr. Frederick Resch and Dr. Hugh Bennett, Youngstown, Ohio.

Present address: The Columbus Medical Center 1211 Dublin Road (8).

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Thyrotoxicosis Simulating Hyperparathyroidism

R. A. PRIBEK, M.D., and R. C. MEADE, M.D., Wood, Wis.

Introduction

Stanley and Fazekas,[1] in 1949, first reported as case of thyrotoxicosis the manifestations of which closely simulated hyperparathyroidism. Following therapy with propylthiouracil, the symptoms of hyperparathyroidism subsided as the patient returned to a euthyroid state. Rose and Boles,[2] in 1953, reported three additional cases of thyrotoxicosis which simulated primary hyperparathyroidism. In view of the apparent rarity of this association we deemed it of interest to report an additional case.

Report of Case

The patient, a 30-year-old white man, commercial fisherman, entered the hospital on Aug. 3, 1956. He stated that he had been in good health until approximately two and one-half months prior to admission, when he first noted diaphoresis, heat intolerance, and vague pains in the cervical and lumbar spine. Shortly thereafter he developed anorexia, nausea, vomiting, and generalized crampy abdominal pain. Subsequently he noted tinnitus, frontal headaches, polydipsia, urinary frequency, and muscular weakness, especially on climbing stairs. He estimated that he had lost 35 lb. since the onset of his illness. Medical attention was first sought one month after the onset of symptoms. An elevated temperature was found at this time by his private physician, who treated the patient with oxytetracycline for three days. Two weeks previous to his admission to this hospital he was evaluated at another hospital. Examination there revealed a well-developed thin white man, who appeared tired, weak, depressed, and acutely ill. Physical findings included a nodule in the right lobe of the thyroid, severe myasthenia, tachycardia of 140, tremor of the extended fingers, warm moist skin, and evidence of weight loss. The hemogram, urinalysis, BUN, liver-function studies, and agglutinations for typhoid, paratyphoid, and Brucella were reported as normal. Stool studies for ova and parasites and urine studies for porphyrins were negative. Complete roentgenographic studies of the gastrointestinal tract including a cholecystogram were interpreted as within normal limits. The BMR was +24%. Serum calcium and inorganic phosphorus determinations were 11.7 mg. and 3.7 mg. per 100 cc., respectively. The before-mentioned gastrointestinal symptoms increased in severity despite dietary and medical management. Thyrotoxicosis was considered because of myasthenia, tachycardia, weight loss, tremor, and thyroid enlargement. He was transferred to this hospital for confirmation of diagnosis and further evaluation.

The patient's past history was not remarkable except for a complaint of long-standing "nervousness." His mother had had thyroid surgery for a goiter. Further information concerning the type of thyroid disease was not obtainable.

The physical examination on admission to this hospital revealed a well-developed asthenic white man, who appeared weak and depressed. The pulse was 96; respirations, 20, and the blood pressure, 136/84. The skin was warm and dry. Findings on examination of the head and neck were normal, except for slight enlargement of the thyroid gland. The right lobe was more prominent than the left. Findings on examination of the heart and lungs were normal. The abdomen was soft and nontender. No masses or organs were palpable. A fine tremor of the outstretched hands was noted. Marked muscle weakness was evident from the patient's gait.

Laboratory studies disclosed a normal hemogram. The sedimentation rate was 55 mm. per hour by the Westergren method. Multiple urinalyses revealed only a persistently low specific gravity. A qualitative urinary Sulkowitch test showed a moderate amount of precipitate. Phenosulfonphthalein excretion was 27% in 15 minutes and 65% in 1 hour. Urea clearance was 46% of average normal. A basal metabolic rate was +35 and +29, with a pulse rate of 90 per minute. Serum cholesterol was 197 mg. per 100 cc., with a normal ester fraction. Nonprotein nitrogen was 48 mg. per 100 cc. The fasting blood sugar and liver-function studies were normal. Initial calcium and inorganic phosphorus determinations were 13.8 mg. and 3.9 mg. per 100 cc., respectively.

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From the Department of Internal Medicine, Veterans' Administration Center, Wood, Wis., and Marquette University School of Medicine, Milwaukee.

The alkaline phosphatase determination was normal. Subsequent serum calcium determinations were 14.1 mg. and 14.2 mg. per 100 cc., with corresponding inorganic phosphorus value of 4.1 mg. per 100 cc. The 24-hour urinary calcium excretion was 786 mg. with a calcium intake of approximately 200 mg. per day. This excretion was considered to represent an elevation of two to three times normal. A bone survey showed no evidence of skeletal demineralization. X-rays of the teeth showed normal lamina dura. Renal calculi were not demonstrable on a scout film of the abdomen.

The patient's hospital course was characterized by marked prostration and persistent nausea, vomiting, and abdominal pain, which failed to respond to a bland diet, antispasmodics, and sedation. It was necessary to maintain nutrition by parenteral feedings. A diagnosis of thyrotoxicosis was considered. The severe and persistent symptoms of anorexia, nausea, vomiting, and abdominal pain were difficult to explain. The finding of a markedly elevated serum calcium suggested that these symptoms were attributable to hypercalcemia. Primary hyperparathyroidism was suspected, but the diagnosis seemed unlikely in the presence of a normal serum inorganic phosphorous. He denied using vitamin D, calcium salts, and absorbable alkali. There was no x-ray evidence of the bone lesions which may be associated with hypercalcemia. With a large fluid intake the serum calcium remained elevated and the NPN decreased to 38 mg. per 100 cc. It was necessary to delay a serum protein-bound-iodine determination and I^{131}-uptake studies because of a recent cholecystogram; therefore a tentative diagnosis of thyrotoxicosis with hypercalcemia was made, and the patient was given a therapeutic trial of 400 mg. of propylthiouracil daily.

After six weeks of antithyroid therapy he was markedly improved. His gastrointestinal symptoms abated, and he gained 30 lb. Mild "nervousness" persisted. The serum calcium decreased to a normal level of 10.7 mg. per 100 cc. Inorganic phosphorus, nonprotein nitrogen, and alkaline phosphatase determinations were also normal. He continued propylthiouracil therapy for an additional four weeks, with no change in his "nervousness." Laboratory studies remained normal. The propylthiouracil was discontinued in preparation for a more extensive thyroid evaluation. The I^{131} uptake studies performed three weeks later confirmed the clinical impression of hyperthyroidism. The 24-hour I^{131} uptake was 61.5%. A therapeutic dose of 5 mc. of I^{131} was administered at this time. Two months after the I_{131} therapy he returned complaining of recurrent tremulousness, diaphoresis, and palpitation of two weeks' duration. There were no gastrointestinal complaints. The skin was warm and moist. There was a minimal unilateral exophthalmos. The thyroid was diffusely and moderately enlarged. There was a fine tremor of the extended fingers. It was the clinical impression that the patient was still thyrotoxic, and this was confirmed by a protein-bound-iodine value of 11.1μg. per 100 cc. and an I^{131} uptake of 62.5%. The serum calcium remained normal at 10.5 mg. per 100 cc. Inorganic phosphorus, alkaline phosphatase, urinalysis, and renal-function studies were all normal. He was again treated with 5 mc. of I^{131} and discharged.

Comment

It is well established that an increased urinary and fecal excretion of calcium may be associated with thyrotoxicosis.[3,4] In severe or long-standing cases this may lead to to skeletal demineralization.[5,6] The serum calcium level in this condition is usually normal, but an elevated calcium with a normal inorganic phosphorus level has been noted.[7-9] Symptoms secondary to the hypercalcemia, however, are apparently rare, judging from the paucity of reported cases.

In the case herein reported the prominent symptomatology consisted of anorexia, nausea, vomiting, abdominal pain, severe myasthenia, prostration, and mental changes. These were assumed to be manifestations of hypercalcemia. It has long been recognized that pronounced gastrointestinal complaints may accompany thyrotoxicosis,[10-12] especially the severer cases or during frank crisis. These complaints likewise are frequently associated with the hypercalcemia of hyperparathyroidism, as reemphasized in a recent report.[13] In the above-mentioned reports of gastrointestinal complaints accompanying thyrotoxicosis serum calcium levels were not recorded. It would be of interest to know if hypercalcemia existed in these and similar cases. Stanley[8] has suggested that the possibility of hypercalcemia should be considered in all cases of thyrotoxicosis with prominent symptoms of nausea and vomiting.

The mechanism of the increased calcium and phosphorus turnover in thyrotoxicosis remains obscure. Aub and associates,[3] in 1929, demonstrated an eightfold increase

in urinary calcium excretion in patients with Graves' disease. They also found a less pronounced increase in calcium excretion in patients with toxic adenomata and in those receiving exogenous thyroid hormone. Conversely, in myxedema they found a diminished urinary excretion of calcium. They postulated that the thyroid hormone, while increasing all tissue metabolism, might stimulate the parathyroid tissue to overactivity. This theory was discarded owing to the absence of hypercalcemia in the cases studied. In a later study Aub and associates [14] showed that the administration of thyroid hormone increased the serum and urinary calcium in patients with hypoparathyroidism. They were able to relieve hypoparathyroid tetany with thyroid hormone alone. Cope and Donaldson,[15] in 1937, reported a patient who developed hypocalcemia and tetany following inadequate subtotal thyroidectomy for hyperthyroidism. With the recurrence of hyperthyroidism the tetany was relieved and the serum calcium rose. After potassium iodide therapy hypocalcemia and tetany reappeared. These observations would indicate that thyroid hormone alone can elevate the serum calcium and that coexisting hyperparathyroidism is not necessary to explain the hypercalcemia sometimes associated with thyrotoxicosis.

Six cases of simultaneous hyperfunction of the thyroid and parathyroid gland have been reported. In only three of these six cases [16-18] was histological evidence of both diseases obtained at operation. Two of the remaining three cases [19,20] were treated surgically for hyperthyroidism, but a parathyroid tumor was not found. The other case [21] refused surgical exploration. Only the three patients who had definitive parathyroid surgery had relief of symptoms attributed to hypercalcemia. In our case this was accomplished with propylthiouracil therapy alone.

Aub and associates,[3] in 1929, suggested that thyroid hormone might exert a direct stimulating catabolic effect on the calcium deposit in bone. They stated that this would be in agreement with the general action of thyroid hormone on other body tissues. At present there is no conclusive evidence to prove or disprove this attractive hypothesis. These investigators also demonstrated that an elevation of basal metabolism alone does not cause an increased calcium excretion. Three of their four cases with an elevated basal metabolism due to fever or leukemia had normal calcium elimination.

Recent studies by Krane and associates [22] with intravenous radioactive calcium demonstrated that serum Ca^{45} levels declined more rapidly in thyrotoxicosis and Paget's disease and less rapidly in myxedema as compared to normal. They concluded that bone formation and destruction was proceeding at an increased rate in thyrotoxicosis. They suggested that the increased calcium turnover in both thyrotoxicosis and Paget's disease may be related to increased bone blood flow.

A mechanism of mild renal impairment has been postulated to explain the rare finding of hypercalcemia in thyrotoxicosis.[7] It has been suggested that the impaired kidney, while capable of excreting more than the normal amount of calcium, in this situation can not clear the excessive load presented to it. This mechanism assumes as the primary event an increased mobilization of calcium resulting from excessive bone catabolism. With adequate renal function hypercalciuria without hypercalcemia would exist. For renal impairment to cause hypercalcemia a decreased glomerular filtration or excessive tubular reabsorption of calcium would have to occur. The latter mechanism seems rather unlikely, and the fact that in our patient the NPN fell to normal with hydration while the serum calcium level remained elevated speaks against a diminished glomerular filtration as the mechanism responsible for the hypercalcemia. That renal function may be impaired in this condition is suggested by the presence of azotemia in our case and three of the four previously reported cases. This

finding my represent nothing more than dehydration from protracted nausea and vomiting.

Summary

A case of thyrotoxicosis simulating primary hyperparathyroidism has been presented. Severe gastrointestinal symptoms of anorexia, nausea, vomiting, and generalized abdominal pain which were attributed to hypercalcemia completely disappeared with propylthiouracil therapy. The serum calcium returned to normal levels, where it remained despite a persistent thyrotoxicosis. The theories of altered calcium metabolism in thyrotoxicosis are discussed. At present there is no satisfactory explanation for the occasional finding of hypercalcemia in thyrotoxicosis.

Veterans' Administration Center.

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Review of Neuropsychiatry

STANLEY COBB, M.D., D.Sc., Cambridge, Mass.

Sir Charles Putnam Symonds, leading British neurologist, retired last year from his post as neurologist to Guy's Hospital, where he had served for 25 years. His record in neurology is long and distinguished. He has illuminated our knowledge of encephalitis, focal infections of the brain, cerebral trauma, and hereditary and degenerative diseases. He made a brilliant record in World War II in the Royal Air Force, was elevated to the rank of Air Vice-Marshall, and was knighted. In this work he was both neurologist and psychiatrist, reflecting his early interest in psychiatry, shown by his training at the Phipps Clinic, in Baltimore, under Adolf Meyer. He has always believed that the two disciplines should come closer together and has deplored (with me) the recent tendency for separation between the two. In his honor the first number of *Guy's Hospital Reports* for 1956 [1] was made a special number devoted to neurology, especially oriented toward the demyelinating diseases and containing several important papers on neurochemistry. Dobbing [1] discusses the blood-brain barrier as a problem in physical chemistry, not as a tissue. Wright [1] gives evidence from recent isotope experiments that viruses and neurotoxins are conveyed up the spinal cord not in the axones, as was formerly thought, but in the extracellular fluid. Four papers on different aspects of neurochemistry, including metabolism, enzymes, and energetics, make a solid contribution to modern neurology and emphasize the trend toward chemistry, which Sir Charles had always pointed out in his teaching.

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Neurochemistry

Another indication that chemistry is coming into its own in relation to the nervous system is seen in the fact that four books have been published within two years on neurochemistry. Moreover, a professor of neurochemistry has been appointed at the Harvard Medical School—Dr. Folch-Pi, whose recent research on lipids and proteins of the brain has been fundamental and fruitful. Of the four books, the one by McIlwain [2] is a textbook giving a good introduction to the subject. Elliot, Page, and Quastel,[3] in their volume, have brought together authoritative chapters from many authors. The books by Korey and Nurnberger [4] and by Waelsch [5] are reports of meetings at which papers on neurochemistry were presented, Waelsch's compilation dealing largely with the chemistry of the ontogenesis of the brain.

In this review last year [6] the main subjects discussed were the pharmacology of the nervous system and the clinical effects of the new "tranquilizing" drugs. If little space is given to this field in the present review, it is not because little has been produced. On the contrary, the flood of "literature" on the "tranquilizers" continues; the brochures become ever more elegant and their claims are just as unconvincing, even though they are backed up by clinical papers published in highly respectable journals. If one wishes to get a more critical evaluation, he should read two recent papers. One of these is by Gerard,[7] in *Science*, and be-

gins by saying: "The phrenotropic agents, and conferences about them, have become drugs on the market. Three out of ten prescriptions in this country are now for 'tranquilizers,' more than a billion meprobamate tablets alone have been ordered by their physicians for 160 million Americans in a little more than a year. . . ." The second is a paper by Wolf [8] published as a monograph by the American Psychiatric Association. This 23-page pamphlet reviews the methods used to investigate and evaluate therapeutic agents, with special reference to the "tranquilizing" drugs. The author is quite explicit in showing why he does not believe in papers based on clinical impressions. He states that double blind controls are essential to protect us from the welter of favorable reports in the literature. He gives good evidence to show that placebo control must be blind, because drug therapy backed up by the enthusiasm of the physician may result in bodily changes that have nothing to do with the drugs exhibited.

It cannot be denied, however, that reserpine, chlorpromazine, azacyclonal, and meprobamate have important effects on the central nervous system.[9,10] The four drugs apparently affect the nervous system in quite different ways but with somewhat similar beneficial effects in states of anxiety and tension. The rauwolfia alkaloids (e. g., reserpine) are said to cause their pharmacological effect by releasing serotonin in brain tissue.[11] This remarkable compound is 5-hydroxytriptamine. It was discovered by Page,[12] as a vasoconstrictor in the blood serum, in 1947. In 1953, Twarog, in Page's laboratory, and Gaddum,[13] in Edinburgh, discovered independently that serotonin occurred in relatively large quantities in the brain. It has now been shown to be localized in its distribution, there being much in the hypothalamus and midbrain and little in the cerebral cortex and cerebellum. Welsh, who did much of the early work on serotonin in the invertebrates, considers it a neurohumoral agent.[14] It is probably as important as such substances as acetylcholine, epinephrine, and arterenol. Much work is being done in many laboratories, as is attested by the remarkable group of investigators brought together to discuss the pharmacology of the psychotomimetic and psychotherapeutic drugs at the New York Academy of Sciences.[12] Some of the workers go so far as to already believe that serotonin plays a significant role in schizophrenia and that it is antagonistic to atropine and lysergic acid, both of which cause hallucinations. Woolley and Shaw [15] have shown that by inhibiting serotonin in human subjects they can cause episodes not unlike schizophrenia, and more recently Woolley [16] has developed a method to increase the functioning serotonin in the brain. This is said to have improved schizophrenic patients in preliminary tests.

Hoffer [17] has been working for years on various epinephrine derivatives and their potential relationship to schizophrenia. He believes that, as a working hypothesis, one can consider the oxidized derivatives of epinephrine as etiological factors in schizophrenia. Adrenochrome and adrenolutin are toxins which interfere with cerebral metabolism. They are produced when autonomic activity is increased and epinephrine is detoxified. Although the clinical applications of all this work are still experimental, the trend of the investigations gives hope that an understanding of the chemical processes involved in some of these psychotic disorders may soon be attained.

Behavioral Science

Most of us who have lived long enough to become professors and editors have become conservative and find it hard to accept change as a good thing; but change is necessary and inevitable. Since 1950 strange words have been appearing in the literature of neurology and psychiatry—"cybernetics," "communication," "information theory," "behavioral science," "entropy," and "feedback," to mention only a few. Indeed, we have been invaded by the engineers with their computing machinery and automation

on the one hand and by the sociologists with new ways of observing and recording behavior on the other. Even if the editor of *Brain* [18] preaches and tries to keep us out of entangling alliances by treading the straight and narrow path, and even if many psychiatrists urge orthodoxy, it looks as if a concept has been formed which may lead to important theoretical reconstructions and new methods of attack on practical neurological and psychological problems.

At Ann Arbor there has been formed in the University of Michigan a Mental Health Research Institute which now publishes as its organ a journal called *Behavioral Science,* edited by a "multidisciplinary" board of distinguished men in psychology, psychiatry, neurophysiology, anthropology, mathematics, and sociology. Four numbers have been published during 1956, with many papers of interest to neurologists and psychiatrists. There are relatively simple ones, such as "Toward a Theory of Schizophrenia" [19] and "Mind-Body Dualism and the Unity of MindBody," [20] and some difficult ones, such as "A Calculus for Ethics," [21] which is written in a mathematical language far beyond the grasp of most neuropsychiatrists. Perhaps the place to begin is with the editorial in the first number of *Behavioral Science;* this should be followed up with "Behavior Theory and the Social Sciences." [22] Another solid production by men thinking along these lines is a book reporting four symposia, edited by Grinker and entitled "Toward a Unified Theory of Human Behavior." [23] These are publications we cannot ignore because they may be the beginning of a "major breakthrough" in our long stalemate in psychiatric research. To show some skepticism is only natural, and one review [24] says of the latter book, "Some say this is an untoward movement; some say not. However that may be, the facts are that it is so delicately balanced between importance and grandiosity that it has already been impaled upon a partially deserved parody."

I could not review this literature if I would. I can only point out that here is a trend that may have far-reaching future results. To give a much simplified view of the sort of schema employed, I quote Shands [25]:

> The process of adaptation is inextricably bound up with the process of communication. Adaptation requires both (1) a sensitivity to changing conditions and (2) a responsiveness by means of which to meet these changing conditions. The former is basically sensory in nature while responsiveness is basically motor. In response to a sensory input a motor output occurs. An adapted system is one in which each input has an appropriate relation to an output. . . . The relation between an "open" system which is adapted to, or operates in communication with, a larger system can be described in two processes: The first is an analysis of input, i. e., the discrimination of form, the second that of an output, i. e., some movement in relation to the form. A paramecium, for example, discriminates between food and a carmine particle by accepting the one and rejecting the other. These two processes of *form discrimination* and of *responsive movement* are basic respectively to intellectual analysis and to affective responsiveness. . . . Recent developments in the field of communication theory offer a powerful tool which promises much in this area. This tool is the notion of *information* in its technical sense.

If these new bedfellows can inseminate us without causing morning nausea by their jargon, neologisms, and complexity, much might come of the relationship. But communication must be left simple and direct because part, at least, of the motivation of this new movement arose as a reaction against the vagueness and lack of adequate control in the clinical methods of the psychoanalysts. This new behavioral science has little to do with the "Behaviorism" of 30 years ago, which had no use for mental reactions, consciousness, or anything human and was, in fact, what Roback [26] aptly called it, "psychology out of its mind." Much has been written about the "output" side of behavior, much less about the "input." In the latter part of this review (after taking up Judson Herrick's remarkable synthesis, published in his 88th year) I shall consider the new work on central modulation of sensory perception.

"The Evolution of Human Nature"

The appearance in October, 1956, of a new book by C. Judson Herrick [27] is an

event in the neurological world of no small magnitude. Its implications for psychiatry are equally great because Herrick's main interest is psychobiology. He discusses what the mind is and how the mind works on the basis of his 60 years of research in comparative anatomy. The book is a remarkable synthesis, expounding the mature philosophy of a great teacher, expert in a special field and interested in all biology. It presents no new data but discusses in an illuminating way the extraordinary advances of the last two decades. Coming at a time when neurology and psychiatry are tending to draw apart and split into temporary "schools," it emphasizes the great problems of mind, consciousness, memory, value, and symbolism as seen by a student of cerebral anatomy.

Herrick's "The Evolution of Human Nature" is a book of 506 pages divided almost equally into two parts. In Part I he critically analyzes certain factors of behavior and evaluates them in terms of animal and human development. Since the nervous system is the dominant apparatus for the regulation of behavior, Part II is concerned with summarizing the evolution of the nervous system, the characteristic features of nervous functions, and the biomechanics of mentation. Principles of psychobiology are discussed in both parts and are brought in appropriately to make the whole a readable and convincing exposition of these most important and difficult problems. The author's interest and knowledge in many fields is remarkable, and his tolerance is exceptional; he takes the best from many "schools" and does not bother with the trivialities of those who feel impelled to be "anti" this or that.

He is a convinced monist and believes that the dualistic hypotheses, such as the theory that mental acts are nonphysical processes, are untenable and close the door to further scientific inquiry. He believes that human mentation is dependent upon physiological processes that can be studied, and his attitude as a modern behaviorist allows him to study all components of the vital processes that eventuate in conduct, "subjective" as well as "objective." He realizes the great importance of studying human motivations. For example, he says:

> Human nature has developed from animal nature, but a man is something more than a brute. The true measure of man is the pattern of performance; and this pattern is determined far more by wishes, hopes, and fears than by an external environmental influences. This is not a philosophical speculation. It is a fact of everyday observation confirmed by biological and psychological analysis of motivation.

It is evident that Herrick understands modern dynamic psychology and the contribution of the social sciences. Chapter 15 shows that he has read the sociologists from Allee to Yerkes and Zuckerman and has added to his own expert knowledge of the vertebrate nervous systems an understanding of the personal and cultural factors of human organization with their various blends of instinctive drives and ideologies. Chapter 12, "Evolution of Value," is equally forward-looking. He considers value as an objectively verifiable phenomenon. It can be traced in the evolutionary series; a growth of value judgments can be seen in the development of every child. This allows human motivation to take its appropriate place among other biological functions, and the study of these motivations, conscious and unconscious, is of first importance in understanding social behavior.

The whole book is directed at the understanding of mind, so it is impossible to compress Herrick's conception to a few pages or paragraphs. Chapter 22, "Mental Functions," and Chapter 23, "A Biological Analysis of Mental Processes," are especially pertinent. He considers that mind is awareness and that it becomes more and more important as a function as the complexity of the brain increases in the ascent of the phylogenetic ladder. "The body makes the mind . . . it is the body in action" (p. 296). His monistic belief is reiterated when he calls dichotomies sterile and unscientific. Traditional materialism, idealism,

animism, and vitalism have been tried and found wanting. I quote from page 286:

> The idea that mind is an entity detachable from the bodily organization that generates it and experiences it must be rigorously excluded from all scientific inquiry. Such a mind cannot be an *agent* in behavior, nor can it be regarded as *the* cause of any behavior. Nonetheless, mentation *as a vital process* has a significance for behavior whether the inquiry is conducted from the standpoint of biology or of psychology. An animism recognizing both that mental processes as subjectively experienced are real events which influence conduct and that search for the mechanisms employed in these transactions is a prime function of physiological psychology has no mystical contamination whatever.

The evolutionary history of mind is important in our understanding of consciousness. The field theory regards mentation as a vital process carried on in a field of metabolic activity. Mind cannot be regarded as an entity separable from its field of operation. The mind and the field are inseparably one (p. 266). But, phylogenetically, when the mental process reaches the level of self-consciousness and the organism is conscious of self as actor, it cannot be conscious of the field of activity as a part of the same unit. In the author's words (p. 295):

> The clear-cut polarization in consciousness of perceiving subject and perceived object is perhaps a methodological artifact arising from the inherent limitations of the finite mind and the practical use we make of introspective and extraspective experience. This is supported by the fact that it seems to appear rather late in human psychogenesis. Structure can be known only indirectly through sensation and movement in space and time, and what can be learned in this way is determined by the structure of the organs used. Our conceptual mental processes are set in a different frame of reference and use a type of nervous structure which has properties quite different from those employed in sensory and motor analysis. This is the reason why mind and matter cannot be directly equated in terms of any presently available units of measurement.

The distinction between analytical (sensory and motor) and integrative (conceptual) functions of the nervous system is a fundamental difference repeatedly emphasized throughout the book. The phasic analytical functions are performed by the simple, more stable neuronal configurations. The integrative functions are carried out by widespread assemblies of neurons, where the firing of any one assembly may serve as a signal for the activation of one or more other assemblies. Here one approaches such problems as the cerebral basis of memory. The activation of any assembly of nervous elements leaves a trace which facilitates the reactivation of that system. The nature of that "trace" is not known (p. 435). The analogy of the computing machine is used, and the brain is considered as a glorified sorting machine capable of abstracting generalizations. On page 448 he concludes:

> The marvelously efficient electronic calculators are not thinking machines. They have great heuristic value for neurology because they furnish unique opportunity for study of some mechanical principles of wide import. But let it not be overlooked that these principles may find expression in a great variety of mechanical structures, and no dead mechanism which has been made or conceived can serve as an adequate model of the incomparably more elaborate apparatus of living cortical tissue. The only way to find out how the brain works is to study the brain itself.

Signs, signals, codes, and symbols are discussed in Chapter 31. In animal evolution there is a progressive elaboration of the apparatus of sorting and communication; this is manifest in behavior. The patterns range from responses to simple signs to the inconceivable complexity in the elaboration of symbols demonstrated in human thinking and conduct.

Lastly, one must mention causation, because for Herrick a mechanism of any kind is a means for getting a product. The living body, like every other mechanism, has no meaning apart from the ends toward which its behavior is directed. Much animal behavior is controlled by signals from the goal toward which it is directed. This feed-back is a kind of mechanical teleology, but in science the idea of "teleological causation" must be excluded because this involves action of the future on the present. Yet all adaptations have a future reference; an end is to be achieved, and this implies some kind of natural teleology.

Taken as a whole the book is exceptionally well written, clear, and orderly, with a summary at the end of each chapter and less important discussions of detail put in fine print. Much of it is certainly difficult reading because unsolved problems about which we have insufficient data are boldly approached. In any such book there must be points with which the reader does not agree; most of these can be resolved as matters of definition. The emphasis on the conscious process as a total pattern is illuminating when taken with the evidence that the nervous processes involved are circular reactions with "feed-back." But one finds it difficult to agree with the statement that the integrated activity in the brain has been "proved by abundant evidence" to be in the form of "tuned resonating circuits." Nor does one agree that Pitts and McCulloch have constructed their models "on the basis of known histological structures of the brain." These are still just good theories.

Consciousness and unconscious processes are so much talked about in psychiatry that it would perhaps be well to point out that the type of process that is confined to the lower levels of the nervous system and never reaches consciousness makes up a great part of our nervous activity—that part which is automatic, involuntary, and reflex. This has nothing to do with the "unconscious process" of the psychoanalysts, which is highly integrated, once conscious, and repressed.

The Reticular Formation

One major omission in Herrick's book is at first surprising. There is no mention of the reticular formation, the "activating system" of Magoun, which has brought so much new knowledge to neurology that there have already been two international meetings on the subject.[28,29] It was discussed in this review in 1953[30] and 1955,[6] but since then a great deal of new work on this neuronal system has appeared. Probably Herrick left it out because most of his new book was written before Magoun's experimental work was first published (1949) and before Magoun, Jasper and Penfield, Adrian, Bremer, Gastaut, and all the others reported in the international meetings in 1953. All this work has much to do with "consciousness" and the physiology of mentation. For a comprehensive understanding of the field the reader is referred to the original reports. In brief, it may be said that the great change in neurophysiological thinking brought about by this work is because of the advance from the reflexology of Sherrington to the new concept of a special system of neurons with the function of general integration. The intricacy of the intercalated systems of neurones discovered in these investigations gives basis for a dynamic conception of memory, awareness, attention, and consciousness. As for the latter, Professor Fessard[28] made a keen contribution when he suggested that "consciousness" was "experienced integration," and he pleased me by quoting my opinion that "mind" is the integration itself. When this integration becomes more and more complex through eons of cerebral phylogenetic development, it is experienced and the phenomenon of "consciousness" begins. It can be proved to be present in man only by personal experience, but it can be inferred by the behavior observed in other men and other animals.[31] Lashley[32] discussed the concepts of "mind" and "consciousness" at the first conference; in fact, he has been thinking and writing about these subjects for 40 years. His latest, and one of his most concise, formulations was given at the meeting of the Association for Research in Nervous and Mental Disease, December, 1956, in a paper titled "Mind as Neural Activity." He said:

> As long as mind is thought of as a special kind of being, obeying an all-or-none law in its presence or absence, or as some special type of energy, such as Sherrington sought and failed to find, so long will its relation to the brain be incapable of investigation. Mind is a complex organization held together by interaction of processes and by the time scales of memory, centered about the body image. It has no distinguishing features other than its organization. The mental

phenomena must be subjected to an analysis as complete and detailed as that which is being made of neural activities. Only as progress is made in such an analysis and as the picture of the brain's activities is completed, will it be possible to make significant correlations between the two organized systems. Meanwhile, there is no logical or empirical reason for denying the possibility that the correlation may eventually show a complete identity of the two organizations.

Agnosia

At the same meeting Denny-Brown and Chambers [33] gave a paper titled "Parietal Lobe and Behavior," in which they made an important contribution to the understanding of agnosia. This concerns a special form of disturbed consciousness in which there is an alteration of behavior with varying degrees of awareness of the behavioral defect; for example, a patient may be unable to recognize his own left hand. As long as such surprising phenomena were thought of in terms of "body image," little understanding of the physiology was possible. But when it is realized that consciousness is a function on the sensory, or input, side of our nervous mechanism and that agnosia is a disturbance of perception at a highly integrated level where symbols are concerned, then the clinical phenomenon becomes more understandable. For a disturbance at a somewhat lower level of perceptual integration the authors use the term "amorphosynthesis," the lack of ability to put together data concerning perceptions of one's own body. This affects the opposite side in lesions of one hemisphere, but agnosia occurs when the leading hemisphere is affected and confuses the picture, making the amorphosynthesis difficult to demonstrate.

Perception and Feed-Back

Our concepts of psychological reactions are slowly becoming more scientific by correlation with neurophysiological data. Nineteenth-century psychologists were good observers of human behavior, like field naturalists, but with improvement of techniques and scientific sophistication they began to study the physiology of the sense organs and the reflex arcs in the spinal cord. The "S-R psychologists" then had a period of ascendency, when behavior was described in terms of stimulus and response. Explaining behavior by conditioned reflexes was the highest development of this trend.

The theory and practical application of negative feedback is an old story to physicists. It did not impress neurologists until "cybernetics" came into existence in 1948.[34] Then it became apparent that the stimulus-response concept is far too simple. Neurological studies from this point of view showed that the central nervous system takes back a certain amount of output as an input; this acts as a control over motor output, indicating a neurological mechanism for seeking a goal. This makes purposive behavior a valid object of scientific study.

Recently evidence has been obtained by several neurophysiologists, using refined electroencephalographic techniques, indicating that the input through the sense organs is under the control of the central nervous system. It has long been known to anatomists that fine centrifugal fibers ran to the sensory organs of muscle, the "spindles." Centrifugal fibers have been described in the optic nerve, the cochlear nerve, and the olfactory bulb. Kuffler and Hunt [35] confirmed and expanded the earlier work of Leksell, in Sweden, to show that centrifugal impulses down the fine fibers to the muscle spindles moderate the centripetal impulses from spindle to cord. Granit and Kaada [36] went farther and showed that certain centers in the brainstem control the discharge of these specific efferent fibers to the muscle spindles.

Granit's especial interest, however, is the eye. He has shown that stimulation of the reticular formation in the midbrain affects the input from cells of the retina.[37] Dodt [38] has been able to bring convincing evidence that this control over retinal activity is by way of the fine centrifugal fibers in the optic nerve. Galambos [39] has demonstrated a similar control by centrifugal fibers upon auditory receptors, with a center in the

brainstem. Rasmussen[40] described an anatomical pathway 10 years ago and has now worked out the feed-back connections of the auditory systems by physiological techniques. Finally, recent experiments by Kerr and Hagbarth[41] have shown that centrifugal fibers run from the anterior commissure to the olfactory bulb and have a control over olfactory reception.

Central modulation of sensory perception seems to be proved. When one understands this mechanism and superimposes it on the negative feed-back which affects motor output, the workings of the nervous system are shown to have new complexity and a new beauty of design. This makes the stimulus-response concept of psychology seem naïve indeed. The advance in psychological thinking made by the understanding of reflex mechanisms is no longer good enough. The study of reverberating circuits, feed-back controls, and central control of sensory perception not only has made a great advance in the understanding of neurological and psychological processes but has explained the functions of many neuron systems that had been seen for years but never understood. Moreover, it can be maintained, as Shands[25] says, that an understanding of the physiology of perception is the basis of psychology and, hence, of psychiatry.

34 Fernald Dr.

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Evolution of Modern Medicine

This section, which has as its primary purpose a review of the contributions of medical investigators and observers of the past to the present-day concepts of disease, is under the special editorship of Dr. Arthur Bloomfield, 2398 Sacramento St., San Francisco 15.

His editorial in the August, 1957, issue of the A. M. A. ARCHIVES OF INTERNAL MEDICINE, *gives further detail of what it is hoped to accomplish in these articles. Contributions or comments for this section may be sent directly to Dr. Bloomfield, or to the Chief Editor for transmittal to him.*

Rudolph Virchow and Scientific Medicine

L. J. RATHER, M.D., San Francisco

It is no longer necessary today to write that scientific medicine is also the best foundation for medical practice. It is sufficient to point out how completely even the external character of medical practice has changed in the last thirty years. Scientific methods have been everywhere introduced into practice. The diagnosis and prognosis of the physician are based on the experience of the pathological anatomist and the physiologist. Therapeutic doctrine has become biological and thereby experimental science.

—Rudolph Virchow, 1877

In the arresting image which closes his great book, Marcel Proust envisions the aged Duc de Guermantes as a being perched on ceaselessly growing living stilts, a giant plunged in the years and epochs of the past. So must Virchow have appeared to his friends and associates at the beginning of the 20th century, two years before his death. As early as 1847 he had founded the *Archiv für pathologische Anatomie und Physiologie und für klinische Medizin*, that today bears his name. His book, "Cellular Pathology," published in 1858, was without doubt the most influential work on disease to appear in the 19th century. Fifty years after having become a full professor of pathological anatomy at Würzburg he was still tirelessly active in medicine; in 1898 he delivered in English the second Huxley lecture before a distinguished audience of scientists and notables in London. His death, in 1902, indirectly the result of an accident, was marked by the tributes of scientists and public figures from all over the world.

No one who reads Virchow's scientific and philosophical papers can fail to be impressed by the breadth and power of his mind. But those who know Virchow as a scientist and philosopher—let alone those who know him merely as a pathologist—are acquainted with only one aspect of his activity. He was an archeologist who excavated with Schliemann at the site of Troy; the author of a book on Trojan graves, who did his own archeological field work in the Caucasus at the age of 73; an anthropologist and ethnologist who edited the *Zeitschrift für Ethnologie* and whose survey of nearly 7,000,000 school children in 1876 should have buried forever the myth of the blond blue-eyed German race; a linguist who knew English, French, Italian, and Dutch, who worked with Latin, Greek, Hebrew, and Arabic. He was a socially minded man who said that science should speak the language of the common people, who derided nationalism in science; he was active in politics from his youthful days on the barricades in 1848 to his opposition to Bismarck, as leader of the progressive party in the Prussian diet.

Virchow was a Faustian figure whose aim was "no less than a universal knowledge of nature from Godhead to stone"—as he wrote in a letter to his father at the age of

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21. His abilities were even then obvious to his contemporaries. The German medical historian Paul Diepgen [1] quotes a letter written by Leubuscher to Meckel stating that the 24-year-old Virchow had "an undeniable degree of intellectual power and authority, and an astounding ability to keep in mind and integrate all sorts of apparently unrelated observations." The fact is that for Virchow the observations were not at all unrelated. He was the kind of man who sees things in their relationships. Yet he was at the same time the most careful, detailed, and critical medical investigator of his day.

The problem of the proper method of science was one of the first with which he dealt. In Germany the influence of a strongly idealistic philosophy had, in the late 18th and early 19th centuries, led many speculative biologists and medical men to believe that by sheer abstract thought it should be possible to solve the major biological problems. To Virchow, the fatal error of this, the natural-philosophical, school in medicine, lay in an unchecked propensity to erect hypotheses on the basis of the flimsiest kind of evidence and to draw analogies in an unrestrained and uncritical fashion. Virchow wanted to relegate hypotheses to a housebroken state, he wrote, but he was far from wishing to dispense with them entirely or to ban analogies altogether. He simply wanted critical control exercised in the light of a detailed examination of the facts. With a remarkably clear idea of scientific method, avoiding both the halting gait of narrowly conceived Baconian induction and the erratic flights of the less critical nature philosophers, he stated that hypotheses and analogies should be firmly based on phenomena of general occurrence. In this case they could function as entering wedges for further investigation. About two decades later, Claude Bernard was to write that hypotheses were indispensable precisely because they led science beyond the facts and permitted it to progress. Virchow, long before, had said that a hypothesis should be a scientific question, posed with the aid of induction and analogy and based on known scientific laws. The answer was to be derived from the experiment which the properly placed question implied. Experimentation was the court of last resort.

The inflation of *apercus*—brilliant or otherwise—into exclusive medical systems claiming to explain all and everything and threatening recalcitrant matters of fact with excommunication is still with us today, but the systems are implicitly rather than openly expressed. This is a defect, of course, but we may on the other hand credit ourselves with an enormous amount of precise factual information in medicine and the special sciences which contribute to it. Virchow thought that the pressing need of his time was precisely the collection of this kind of data, to be achieved by the careful critical investigation of specific matters of fact—*Detail Untersuchungen*, he called it—and by the suppression of irresponsible theorizing. When one considers the number of conflicting schools in medicine, this reaction is understandable. Walter Pagel,[2] in an informative essay on the speculative basis of modern pathology, quotes the following listing from a slightly older contemporary of Virchow's and a member of the natural historical school, Ferdinand Jahn:

Metaphysicians, Idealists, Iatromechanics, Iatrochemists, Experimental Physiologists, Natural Philosophers, Mystics, Magnetizers, Exorcisers, Galenists, Modern Paracelsian Homunculi, Stahlianists, Humoral Pathologists, Gastricists, Infarct-Men, Broussaisists, Contrastimulists, Natural Historians, Physiatricists, Ideal-Pathologists, German Christian Theosophists, Schönleinian Epigones, Pseudo-Schönleinians, Homeobiotics, Homeopathists, Isopathists, Homeopathic Allopathists, Psorists and Scorists, Hydropathists, Electricity-Men, Physiologists after Hamberger, Heinrothians, Sachsians, Kierserians, Hegelians, Morisonians, Phrenologists, Iatrostatisticians.

In this listing we recognize many friends still among us. Some lead a twilight existence on the fringes of medicine. At least one—the iatrostatistician—has swelled in importance.

Systems, wrote Virchow, were to be avoided until a sufficient quantity of empirical data had been accumulated. This point

of view is widely accepted and certainly valid within limits. Two pertinent comments may be made, however: firstly, the point at which a sufficient quantity of empirical data will be available for the purpose of systematization is apt to recede indefinitely, since it soon becomes easier to accumulate facts than to reduce them to order; secondly, it may be argued that empirical data are never gathered in the absence of a system. Some set of presuppositions about the nature of the world, of man, and of disease will determine the character of the facts accumulated. The system may be contained within the procedure of investigation, rather than explicitly proclaimed as a program. The point at which a sufficient quantity of empirical data seems to be available keeps receding because the data always contain a theoretical element. Consequently, when the concealed systemic or theoretical elements change, there is a need for reinterpretation of the data in answer to new questions that arise as well as a need for additional data bearing on these questions.

Virchow himself developed a system of cellular pathology, basing it, within its limits, quite firmly on careful observation. This system seemed for a while to answer most of the important questions in medicine, or to give promise of eventually answering them. Then, rather suddenly, in connection with a great shift in scientific opinion involving a devaluation of morphology the system began to seem almost worthless to many investigators. The shift should have had less effect than it did, since Virchow's cellular pathology was not simply pathological anatomy, as is so often supposed. In fact, he violently rejected Rokitansky's claim that diseases were at all times open to morphological investigation. Nevertheless, largely owing to technical advances in microscopy and the staining of cells and tissues, which made the application of the morphological method extraordinarily fruitful in the study of disease, cellular pathology was somewhat onesidedly developed and in our day is usually confused with pathological anatomy. It is neither pathological anatomy, a science which can be pursued in the absence of any knowledge of cells, nor pathological histology nor organ pathology. It is a principle which has transformed all of these, however, and in addition a theory of the nature of disease. Virchow was himself very well aware of the limitations inherent in a purely anatomical approach. For how, he wrote in 1849, can one thus "with certainty decide which of two coexistent phenomena is the cause and which the effect, whether one of them is the cause at all, instead of both being effects of a third cause, or even whether both are effects of two entirely unrelated causes?" The difficulties involved in attempting to infer temporal and causal relationships from objects known only in their spatial relationships could hardly be more succinctly expressed.

The position of Virchow in the history of medical thought is most frequently misunderstood by identifying him with proponents of what might be called intransigent anatomicism, i. e., the view that anatomical changes must be at the root of all diseases. Even in Germany, August Bier,[3] writing in 1937, found it necessary to protest against this misunderstanding and to call attention to the fact that Virchow regarded cellular pathology as a biological, not a purely anatomical, theory of disease. In 1938, during a period in which Virchow stood under a cloud because his ideas of race offended Nazi sensibilities, Ludwig Aschoff[4] again protested gainst such misrepresentations. The statement that Virchow's cellular pathology is a biological theory of disease simply means that it treats of disease as a disturbance of the fundamental living unit, the cell. This does not mean that the techniques of physics and chemistry cannot be used in the study of the cell. On the contrary, their use is called for. But even if living things were to be explained in terms of the mechanical results of molecular forces, wrote Virchow, it would still be necessary to designate with some special name the form in which these forces are embodied. Our ex-

perience indicates that life can manifest itself only in a concrete form, bound to certain substantial loci. These loci are the cells. The cell is at once the unit of life and the unit of disease.

The second feature of cellular pathology is the idea of localization. Strictly speaking, Virchow wrote, there are no generalized diseases. All diseases are localizable, since they are bound to cells. Aschoff has argued that Virchow wanted to localize lesions, not diseases, basing his contention on a few lines written in 1854:

> . . . it is certainly consequent to localize diseases (not disease), to assign them specific anatomical seats. . . .[5]

A distinction, not too plain, is made here between *Krankheiten* and *die Krankheit*. If a distinction had been made between diseases as clinical entities and diseases as characterized by cellular lesions, a difficulty that has plagued many medical theorists would not have arisen. Perhaps Virchow merely meant that the subjective aspect of disease was not localizable. In any case, he stated quite clearly in the same paper that the localization of a disease process does not imply that an anatomical or histological change is necessarily present. It was for this reason, among others, that he opposed the great pathological anatomist, Carl Rokitansky:

> The basic error of this (Rokitansky's) point of view rests, in our opinion, on the confusion of the anatomical with the material. We are, as well, in no position to conceive of any kind of living process in the human being, regardless of how functional it may seem, without a material change —however, must it therefore be anatomical? . . . . Every anatomical change is a material one as well, but is every material change, therefore, also anatomical? Can it not be molecular? Can a deep-reaching molecular alteration of the inner composition of matter not take place with the preservation of its inner form and outer appearance? These finer molecular changes of matter are objects of physiology, not anatomy; they are functional—dynamic, if one wishes to use this forbidden expression. The stimulated, functioning nerve is anatomically no different from the latently active "resting" nerve; the structure of necrotic bone may completely correspond to that of living bone. One can have the greatest respect for anatomical, morphological and histological studies, and one can regard them as the unavoidably necessary foundation for all further investigation—but must one proclaim them, therefore, the only ones to be pursued, the ones of exclusive significance? Many important phenomena in the body are of a purely functional kind, and when one attempts to explain these also with a mechanical hypothesis, in terms of fine-molecular changes, it should never be forgotten that the methods for their observation and pursuit can never be anatomical.[5]

The essence of Virchow's conception of disease, then, is as follows: All diseases are reducible, in the final analysis, to active or passive disturbances of groups of living cells—each one derived from a parent cell—whose functional capacities depend on intracellular physical and chemical processes and may be to some extent inferred from morphological changes.

Virchow and the Ontological Conception of Disease

In his two papers, "Standpoints in Scientific Medicine" [6] and "Scientific Methods and Therapeutic Standpoints," [7] published in 1847 and 1849, respectively, Virchow rejects the ontological conception of disease in favor of the physiological conception. Yet in his paper "One Hundred Years of General Pathology," written 45 years later, he states that cellular pathology is

> . . . expressly ontological. That is its merit, not its deficiency. There actually is an *ens morbi*, just as there is an *ens vitae;* in both instances a cell or cell-complex has the claim to be thus designated. The *ens morbi* is at the same time a parasite in the sense of the natural-historical school, net in the sense of the bacteriologists.[8]

What happened in the interim? The answer to this question will disclose the nature of Virchow's achievement.

The distinction between ontological and physiological conceptions of disease can be made clear in a few words. The essence of the ontological conception is the idea that diseases are substantial things (entia, onta), that they have real existence as such. The essence of the physiological conception is that diseases have no existence as such but are merely reflections of deranged function.

Where the ontologist sees discrete entities, each with its own peculiar laws of development, the physiologist sees quantitative deviations from the normal course of bodily function. Now a great many variations on these two themes are possible. The one that offended Virchow in his younger days was the parasitic theory of disease, particularly as developed by the school of natural historians. In this conception, not the etiological agent but the disease process itself was regarded as a parasitic lower life form. A therapeutic corollary was sometimes included. Should there not be a therapeutic entity corresponding to each disease entity? In regard to this, Virchow wrote as follows:

> . . . as soon as one is convinced that there are no disease entities one must realize also that no therapeutic entities can be set up in opposition to them. . . . If disease is only the orderly manifestation of definite phenomena of life (normal in themselves) under unusual conditions, with deviations which are simply quantitative, then all therapy must be essentially directed against the altered conditions. . . .[9]

In this period Virchow seemed to be wholly caught up in the great swing toward the physiological conception of disease, which was taking place in Germany and France. On the occasion of his inaugural address at the Collège de France in 1847, Claude Bernard stated that his task would be to develop the physiological basis on which scientific medicine would rest. In the same year, Virchow wrote as follows:

> . . . the final decision in these matters belongs to a science which at the present time consists only in rudiments, and which appears destined to replace general pathology; I refer to pathological physiology . . . pathological physiology as the fortress of scientific medicine, of which pathological anatomy and the clinic are only the outworks.[6]

In reality, however, he had in his mind a question resting on an ontological presupposition. The question was simply this: where is the concrete disease? Where is its seat?[9] The humoral pathologists had placed it in the fluid, the solidary pathologists in the solid, parts of the body. Neither view satisfied Virchow. Both contained part-truths and did not suffice for the unitary standpoint that he sought for. He was able to reconcile the conflict between the ontological and physiological conceptions of disease by conceiving of disease as life under abnormal conditions on the one hand and by finding the seat of life in the cell on the other. The concrete representation of disease—without which it remained, he wrote, a shadow picture, a formless thing—was then the deranged cell. Once Virchow had become convinced that cells arose only from preexistent cells, rather than from a formless "blastema" as both Schleiden and Schwann had supposed, the old conflict between solidary and humoral views of life and disease became meaningless. The cell had both solid and fluid parts. Life, though a "movement," was bound to a concrete thing, the living cell.

Another form of the ontological view had been cultivated by the natural historical school. This had to a large extent originated with Sydenham, in the 17th century. According to Sydenham, diseases were definite entities, with their own laws of growth, development, and decline, rather than simply random configurations of pathophysiological events. We had as much reason, he wrote,[10] to consider diseases as species as we had plants. The plant springs from the earth, blooms, and dies. The disease does all this with equal regularity. The only puzzling feature for Sydenham was the apparent lack of "substance" in diseases, since they were dependent on derangements of the humors. We can almost imagine Sydenham asking the same question as did Virchow 200 years later: Where is the concrete disease?

Sydenham's entity was a "clinical entity," and Virchow's was to become a "pathological entity" which in the minds of many was to give "substance" to the clinical entity—so much so that without a visible lesion in the tissues a later generation of physicians found it difficult to believe that a patient was really sick.

Variations in the ontological view depend on the kind of being accorded to the entities in question, and the whole problem is a

subspecies of the problem of universals versus particulars. In a crudely realistic (Platonic realism is meant) approach there is the danger of hypostatization of concepts—the ascription of being to things that have no being, which Virchow objected to in 1849 [7]—while in thoroughgoing nominalism there is the risk that diseases will be regarded as convenient fictions. Without the introduction of an element of order into the welter of phenomena observable at the sickbed it would be impossible for the clinician to foresee the future course of the patient under his care and thus to govern his treatment. Although to the layman one sick person seems very much like another, to the eye of the clinician there are definite patterns to be descried, and he has always been reluctant to believe that he himself has introduced the elements of order into the phenomena. He prefers to think that he has only discerned what was already there. Just as the microscopist sees a meaningful pattern of order in his bits of stained tissue, so the clinician sees universal patterns in what seems to the layman a "buzzing blooming confusion," to borrow a phrase of William James.

Linking his work with that of Morgagni in the previous century, Virchow wrote [8] that he had carried to its theoretical conclusion the investigation begun by the former in his "De Sedibus et Causis Morborum." In a logically consequent development of the "anatomical idea" there had been a progression from the correlation of clinical histories with grossly visible anatomical lesions through the conception of tissues as developed by Bichat and finally to the ultimate seat of disease in the living cell. A point had been reached where the knife no longer sufficed for the investigation of the processes taking place in the tissues, and the idea of localization had to be extended to cover invisible inferred physicochemical changes. Clinical entities corresponded to cellular pathological entities, the orderly course of whose events determined the clinical picture. This was Virchow's theoretical triumph.

Virchow and Philosophy

Virchow did not pretend to be an original or profound philosopher, nor did he as a rule pursue his ideas to the bases on which they ultimately rested. Yet it is remarkable to see how explicitly he formulated his views at the outset of his career. The transcendental element in French and German thought and the retreat from Lockean sensualism, which have made the intellectual atmosphere of the European continent so different from that of the Anglo-American countries, apparently had little influence on him. Virchow, it seems, would have been quite at home among the English empiricists. It is easier to imagine him conversing with Mill than Kant. In "Die Einheitsbestrebungen in der wissenschaftlichen Medicin," he states that all human understanding is based on an awareness of the relations of the person to that which lies beyond him, relations that become known as a result of changes excited in the central nervous system by the sense organs. His "neurological" reduction of culture would have satisfied Hobbes and is far more radical than Marx's reduction of culture to a dialectical interplay of the forces of production:

> The complexity of the relationships of the sense organs to the external world, therefore, determines the extent of intellectual activity and the scope of culture. . . . culture, however, consists not only in the scope of sensual awareness, but essentially in the energy of the interrelated excitations of the central apparatus, in the communication of excitations from the sensual receptors to numerous groups of ganglion cells.[9]

Science, according to Virchow, commences with the history of material bodies and then enquires into the mechanisms of their origin and development, into temporal and causal relationships, being more concerned with the processes in which they are involved than with the bodies themselves.[7] Whatever is beyond these material bodies and their properties is transcendent, and the scientist regards preoccupation with this sphere as an aberration of the human spirit. Virchow thus appears to be a materialist at first sight. Eleven years later, however, in a lecture before the *Deutscher Versammlung Natur-*

forscher und Ärzte[11] devoted to the mechanical conception of life, he specifically rejects materialism as a system. It goes beyond our experience and lays the narrow measure of its knowledge on every phenomenon. There may be something beyond experience, he says, but whatever its nature it is no part of the business of science to be concerned with it. The core of Virchow's philosophy of science lies in his insistence on the rule of causality, necessity, and law in all realms of Nature, including the organic world and the human spirit, and his rejection of anything occult or mysterious.

Actually his views on the nature of life did undergo a perceptible change after he began to concentrate all his attention on the living cell, so much so that some of his opponents began to accuse him of vitalism. What happened was that he had discarded the overhasty reduction (made by crude mechanical materialists of his time) of living processes to simple mechanical movements. In reply to Spiess, a prominent "neural" pathologist whom he respected and whose objections he published in his own *Archiv*, he wrote:

> It arouses the concern of Herr Spiess that I have permitted myself the expression "life-force," which I formerly avoided. I have never assumed "special vital forces" as Herr Spiess claims. I do not deny that this has its risks, though not so much on my account as on that of others who think of something quite different from my conception in connection with this word. In the end, however, a term is needed, and it would be impossible to find one that could not be misunderstood or misinterpreted. But nowhere have I even hinted that life-force is primary, or specifically different from the other natural forces: on the contrary, I have repeatedly and emphatically stated the likelihood of its mechanical origin. But it is high time that we give up the scientific prudery of regarding living processes as nothing more than the mechanical resultant of molecular forces inherent in the constitutive particles.[12]

Forty years later he wrote of cellular pathology:

> Nothing prevents the designation of such an attitude as vitalism, except that it should not be forgotten that no special life-force is to be detected, and that vitalism does not of necessity signify either a spiritual or a dynamic system. But, likewise, it is necessary to recall as well that life differs from processes in the remainder of the world, and that it is not to be simply reduced to physical and chemical forces.[8]

Like many scientists of his day, Virchow believed that European civilization had progressed from a philosophical to a scientific age. He had never recovered from his reaction against the nature philosophers of his youth and was apt to conceive of philosophy as armchair speculation. In a lecture read in 1893 he said that more and more people were beginning to understand that science could only progress with the aid of museums, laboratories, and institutes. Experiment was the most important means of forcing Nature to give an answer as to the character, causes, and sequences of a process. No conclusion concerning actual natural processes, he said, had come from the study rooms of the philosophers. Virchow must have known that his own idea of the nature of disease had forced a complete revision of medical thought, and it is a litle saddening to see him trapped into this vulgar philistinism of expression. The ideas of Virchow himself had come from the study rooms of philosophers. He had given them flesh—a worthy task, but not the whole of it.

But there was another, more understandable, facet to his attitude toward loose "philosophizing" of a certain kind. Animal magnetism, spiritualism, hypnotism, racial mystique, and all manner of unhealthy trends seemed to him to be bound up with an antirational speculative view turning in the direction of a dark and unknown side of the human spirit. In the early part of the 19th century the University of Berlin had, for a brief time, two professorships in "animal magnetism." Today, wrote Virchow in noting this, we have spiritualism and hypnotism. Will science be strong enough to guard against the dangers of irrationalism?

> Our age, which is so sure and victoriously happy in its scientific sentiments, just as easily as an earlier overlooks the strength of the mystical urges carried over into the popular mind by various adventurers. It still stands at a loss before the riddle of anti-semitism, of which no one knows what it could wish for in this age of equality before the law, and which, in spite of

this—perhaps even because of it—has a fascination even for the educated youth. Until now no one has asked for a professorship of anti-semitism, but it is said that there are already anti-semitic professors. Whoever knows the story of nature-philosophy in its most radical branches will not be astounded at such phenomena. The human spirit is only too much inclined to forsake the laborious way of orderly thought and lose itself in dreamy reveries . . . . One must learn and become accustomed to explain the unknown from the known, but not, conversely, to choose the dark and unknown, as if it were a new truth, for the starting point toward fantastic conclusions.[12]

Virchow's Conception of Medicine

In 1849 Virchow wrote that he was a humanist and that humanism was based on natural science and most truly expressed in anthropology.[9] Humanism was neither pure spiritualism nor pure materialism, neither egotistical nor sentimentally yielding, neither anarchistic nor communistic. It started from the individual person and recognized the right of every person to his own development. Virchow saw medicine both as a natural science and as the chief of the humanistic sciences. It was for this reason that his interests in medicine, public health, ethnology, anthropology, and politics were not, in his eyes, disparate. He summed up his attitude in 1849, in the following words: Finally, let us recall the words of Descartes, who said that if it were at all possible to ennoble the human race, the means for this could only be found in medicine. In reality, if medicine is the science of the healthy as well as of the sick human being (which is what it ought to be), what other science is more suited to propose laws as the basis of the social structure, in order to make effective those which are inherent in man himself? Once medicine is established as anthropology, and when the interests of privileged individuals no longer determine the course of public events, the physiologist and the practitioner will be counted among the elder statesmen who support the social structure. Medicine is a "social science in its very bone and marrow", as Herr Neuman, with the steely weapon of his sharp logic points out in an essay on the relationship between public health and property—a work small in scope, but far richer in content than anything written prior to his time in this field. No physiologist or practitioner ought ever to forget that medicine unites in itself all knowledge of the laws which apply to the body and the mind. Schlosser is wrong when he attempts to show, in his history of the 18th century, that only belles-lettres and historical literature alter their physiognomy with political change; it is also wrong to believe that, in contrast to the political and religious sciences, the natural sciences can gaze into the deepest wellsprings of knowledge without feeling the desire to apply what they know. Let us recall the saying of Lord Bacon that knowledge is power, and be satisfied with nothing less from our great and promising science of which Hippocrates once said: *Quae ad sapientiam requiruntur, in medicina insunt omnia.*[7] The irony of all this is that Virchow was the only one to fulfill that which he, for the first time, expressed so clearly.

Stanford University School of Medicine, 2398 Sacramento St. (15).

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Books

EDITED BY WILLIAM B. BEAN, M.D.*

The Pathogenesis of Coronary Occlusion. By A. D. Morgan, M.D. Price, $8.50. Pp. 171, with illustrations. Charles C Thomas, Publisher, Springfield, Illinois, 1957.

At a time when the hue and cry of the pack hot on the trail of coronary artery disease drifts and floats about among the fluffy molecules and has its pathway confused, the scent greased by fats and waxed by cholesterol, it is indeed refreshing to have a critical review of a very challenging hypotheses of the pathogenesis of coronary artery disease and infarction of the heart based on morphology. In this book Dr. Morgan gives us a critical survey of Prof. J. B. Duguid's view that coronary artery disease is largely thrombogenic in origin. His document is the more impressive, since at the beginning of the study Morgan was firmly convinced that the hypothesis was wrong. As Morgan says with reference to coronary artery disease, "It should not be forgotten that the preoccupation of the physician is the reestablishment of a circulation that has been arrested by tissue changes, and it is the duty of the morbid anatomist to prevent the chemist from wandering too far away from that small but complex tangle of fibers, cells, and vessels that is responsible for the patient's precarious condition. For this reason, no apology need be offered for employing once again the well-tried approach of the microscope."

The argument runs somewhat as follows: Random sections and serial sections frequently reveal all graduations from a fresh thrombus to an established atheromatous lesion within a short strip of artery. In some instances the natural evolution of a lesion can be strongly suspected, although, of course, morphology can produce an instantaneous and not a moving picture and that too often marred and scarred by all the accumulations of the wear and tear of disease, trauma, and the cumulative corrosions of time upon living tissues and cells.

Several points which rarely come up for much thought are emphasized. They include the remarkable differences between the process and progress of thrombosis in artery and vein and the high molding pressure in arteries which makes the clot have an entirely different structure in arteries and veins. To criticize this book intelligibly would require a long critique of histologic methods and deeper understanding of morphology than I possess. To me the argument is very convincing, though by the nature of the method it eludes final proof. All people working in the field of cardiovascular disease and those who are interested specially in arteriosclerosis and coronary artery disease will find in this book a magnificent display of well-selected and technically excellent pictures of all aspects of coronary arteriosclerosis. They will find marshalled for them a review of the evidence from which they can draw their own conclusions. Even though morphology is no more than one aspect of the general problem, it is often neglected today. We do well to repair to a study of the intimate details of structure which is the fabric of life and the matrix of disease. Morphology must be a court of appeal for our sometimes fanciful speculations in the realm of chemistry, nutrition, metabolism, and some of the less exact if still very exacting components of biology.

WILLIAM B. BEAN, M.D.

Medicine in Virginia, 1607-1699. By Thomas Hughes. Price, 50c. Pp. 78, with illustrations. Virginia 350th Anniversary Celebration Corporation, Richmond, Va., 1957.

Not only is this the Geophysical Year, but despite all the hullabaloo about the Mayflower and such like we should remember that the forebears of our founding fathers of the republic actually got their first toehold in this country on a permanent basis at Jamestown, *Virginia*, 350 years ago. That was long before Plymouth Rock was ever heard of. To those of us who are softened by nipping about from place to place in cars, planes, trains, who in winter live in a hothouse environment and in an artificially cooled one in the summer,

* Communications to this Department may be sent directly to Dr. William B. Bean, University Hospitals, State University of Iowa College of Medicine, Iowa City, or to the Chief Editor for transmissal to him.

and who can practice the best possible contemporary medicine in magnificent hospitals and with every kind of facility, it is interesting to realize how narrow was the margin by which the original colonists held on and how little they had besides fortitude. After visiting Jamestown and Williamsburg this summer and taking a journey to Roanoke Island, where the Lost Colony vanished without a trace two decades before Jamestown held on, I am moved with awe and respect for those bold pioneers who sailed the ocean in their tiny ships and, against all odds of climate, Indians, and illness, staked out the claim on which was erected these United States.

This book, which analyzes Virginia medicine during the first century, reveals that at first the quality of practice probably was fairly high. Then it declined as contact with the mother country grew tenuous, since there was no opportunity for formal training in medicine in the colonies. All the physicians came over after getting their medical education in Britain. Later a few went from the colonies to England or Scotland and then returned. There were only a few physicians, so people who were ill or ailing depended on home remedies or the experience of anyone in the community who would offer advice or suggest medicine. At times ministers of the gospel had as an added charge the care of the sick and the dying. Only toward the end of the century again was there some elevation in medical practice, as the colony stabilized when tobacco began to bring in wealth.

The meager descriptions we have of actual illness which killed eighty to ninety per cent of the earliest settlers are inadequate to judge what the diseases were. Certainly malaria, typhoid fever, and various forms of dysentery were major problems, with accidents, injuries, and infections taking their toll. Nutritional deficiency diseases, which were so acute and catastrophic early in the life of the colony, presumably were minor problems later on.

Almost every new arrival at Jamestown fell sick during the first year with a sickness which was called "seasoning." Probably it represented not one but a host of different infections or deficiency diseases. An account of Virgina written between 1616 and 1618 noted of the settlers that

"They have fallen sick, yet have recovered agayne, by very small meanes, without helpe of fresh diet, or comfort of wholsome phisique, there being at the first but few phisique helpes, or skilful surgeons, who knew how to apply the right medecine in a new country, or to search the quality and constitution of the patient, and his distemper, or that knew how to councell, when to lett blood, or not, or in necessity to use a launce in that office at all."

Thus those who are historically minded and cannot personally make a pilgrimage to Jamestown may for half a dollar get an interesting review of the precarious life of the early colonists, with disease adding to their many difficulties. We must admit the generally ineffectual work of the physicians who treated eagerly but inaccurately those early pioneers. The survivors were those intrinsically tough, or lucky enough to escape the severe illnesses, or rarely get a proper "phisique helpe."

WILLIAM B. BEAN, M.D.

Disabilities and How to Live with Them. Edited by the *Lancet*. Price not given. Pp. 243 Lancet, 7 Adam St., Adelphi, London, W. C. 2, 1952.

It has been said that no one understands a disease until he has had it himself. Though this proverb stretches truth to the breaking point trying to make an aphorism, there is much to be said for a personal illness to give insights. A physician's personal illness should make him more sympathetic. Certainly one does not have to endure all diseases to understand sick persons, but a severe experience may be helpful. Perhaps in another category fall the great cluster of diseases which are discussed in this book about disabilities, a good many being accidents or acute episodes, such as subarachnoid hemorrhage, prolapsed intervertebral disk, broken back, paroxysmal auricular fibrillation, and coronary thrombosis. For the most part, though, this collection of essays, written anonymously, deals with injury or illness of a chronic kind. Since the internist or family practitioner has more and more the care of chronic disease in an aging population, it well behooves him to study the feelings and reactions of the victims of the various processes, injuries, and diseases which run the gamut from blindness and deafness through Parkinsonism, alcoholism, amputations, neuroses, and psychoses, to homosexuality, inborn errors of metabolism, chronic infections, disfiguring injury, and old age. The next closest approach to having a disease or suffering with a deformity is reading what a perceptive person says about it. These

essays were published in the *Lancet* during and after World War II and have been collected in a book which every physician should read regardless of his field of major interest or realm of specialization. Many of the stories are told in simple but feeling terms by laymen. Others are written by physicians who are themselves sufferers from one or another of the various forms of trouble. Somehow reading this book brings to mind the moving lines from Masefield's "Consecration":

"Others may sing of the wine and the wealth and the mirth,
The portly presence of potentates goodly in girth
Mine be the dirt and the dress, the dust and the scum of the earth!
Theirs be the music, the color, the glory, the gold;
Mine be a handful of ashes, a mouthful of mould.
Of the maimed, of the halt, and the blind in the rain and the cold—
Of these shall my songs be fashioned, my tales be told. *Amen.*"

WILLIAM B. BEAN, M.D.

Left-Handed Doctor. By Peter Quince. Price, 16 shillings. Pp. 104. J. M. Dent & Sons, Ltd., Aldine House, 10-13 Bedford St., Strand, London, W. C. 2, 1957.

George Day has presented us with a delightful autobiographical analysis of himself and his patients, the community of medicine, and the time in England before World War II. He writes under the pseudonym of Peter Quince, though just why is a psychological mystery he has not cleared up for us. His medical writings are models of grace and wisdom permeated by deep medical insights. This is a rich and vivid book, written by one of the few physicians who are masters of a prose style which makes reading a delight. The style is so unobtrusive that the reader may not notice its perfection. Only a rare reader will consider the enormous amount of toil and sweat that must have gone into making it so artless, so gay and simple, but at the same time so strong and vibrant with life. It is not so surprising when we know that Quiller-Couch was a major influence in the author's formative years. Only a few words or usages remind us of the subtle but important differences between the American and English languages, e. g., I can never remember how many pounds are in a stone.

The book is about a young physician who goes into a small community general practice in England in the 1920's and his trials and tribulations with the fascinating but sometimes maddening quirks of his loyal but often demanding patients. Nothing of his deep insights and wise affection for his patient is lost by the offhand way in which they are described.

Talent in producing amateur theatricals and a love of music leading to the direction of a group of madrigal singers provided two recreational outlets. They succeeded so well that they became almost impossibly time-consuming. All the hopes and confusion of community players and singers, their struggles and their successes, are portrayed in a cheerful fashion as though told over a cup of tea. Gilbert and Sullivan operettas were performed, almost every one of them, and this book reflects the spirit and sometimes the words of these still popular light operas, which have become embedded in the tradition of English-speaking peoples everywhere. A mature comprehension of the subtle but strong effects of group activity as group therapy, the value of a purpose in life, and the community sense of belonging and participating bore fruit in later medical work.

With the coming of socialized medicine in Britain, the kind of practice described in this book has to a large extent vanished. Well before such changes were imminent the author had to give up his delightful but frenzied life in general practice. These talents for community life all but whelmed him over.

The experience and insights gained in practice came to fruition in the specialization which George Day achieved in running a sanatorium for people with tuberculosis. He organized it as a community enterprise not unlike a choral group or a band of amateur players for whom he was by turns the loving senior member or the stern director. He exploited those elements of corporate life which were so largely wasted or undirected in the kind of medical practice described in Thomas Mann's "Magic Mountain." The author well deserves the distinction and international reputation he has gained for his wise and perceptive combination of constructive aspects of psychosomatic medicine and psychoanalytic insights with surgical and drug therapy in managing the person with tuberculosis. Readers of the "Left-Handed Doctor" will agree that he had a green thumb for patients and will also learn why.

WILLIAM B. BEAN, M.D.

Coronary Heart Disease. By Milton Plotz, M.D. Price, $12. Pp. 353, with illustrations. Paul B. Hoeber, Inc. (medical book department of Harper and Brothers), 49 E. 33d St., New York 16, 1957.

Coronary heart disease, a still not quite satisfactory term for a state of affairs for which we have no exact descriptive label, has quite properly become one of the medical obsessions of our time. Not only are doctors apparently peculiarly liable to the disease but there is no doubt that its actual incidence has risen alarmingly in the past two to three decades over and above what an aging population or an increasingly accurate diagnostic ability of practitioners could have produced. This book by Plotz is surprisingly up to date. It contains much of the current and agitated rumblings about essential fatty acids and cholesterol in relation to coronary artery disease. One of the excellent features of the book is the series of detailed case reports which can be studied with pleasure and profit. Every now and then a cheerful comment creeps into a bleak subject. For instance, with dealing with compensation cases there is a statement that "compensation was allowed in the case of a deputy sheriff who suffered a coronary occlusion while smashing stills in his usual way." While not without faults, this is really an excellent book into which an enormous amount of experience and work have gone. It will be used as an encyclopedia of coronary artery disease. The electrocardiograms reproduced from direct-writing tracings are much less suitable for printing than those made on film. Especially this is an excellent book for someone who will sit down and read it through. Its value is very much reduced by a poor index. For instance, pain is referred to only in one place in the index. There is no mention of syncope, fainting, and a number of other matters, at least some of which are taken up in the text. The bibliography loses much of its value by having no titles. Misprints, fortunately, are rare. In the body of the text there is reference to almost no proper names, which detracts from its historical aspects. One is disappointed that there is little or no reference to the work of Resnik, Blumgart, and Ryle. But such minor points should not detract from a learned book, valuable for undergraduates, house staff, and practitioners.

WILLIAM B. BEAN, M.D.

The Year Book of Medicine (1956-1957 Year Book Series). Edited by Paul Beeson, M.D.; Carl Muschenheim, M.D.; William B. Castle, M.D.; Tinsley R. Harrison, M.D.; Franz J. Ingelfinger, M.D., and Philip K. Bondy, M.D. Price $6.75. Pp. 744, with illustrations. The Year Book Publishers, Inc., 200 E. Illinois St., Chicago 11, 1956.

For internists and those doing general medicine, books of the "Year Book Series" are invaluable in giving a wider panorama of articles than they are likely to get from subscription to any reasonable number of journals. The books in this well-established series are for the most part edited by single persons, but the one in medicine has six outstanding internists, who have divided the corpus of internal medicine into infections; the chest; blood and blood-forming organs; heart, blood vessels, and kidney; digestive system, and metabolism. Some may like to use these books as a quick review. I find them most useful in pointing out articles that I missed, those I wanted to read again, and particularly those from foreign journals which are inaccessible or in a language I can't read. Perhaps the most stimulating and usually the most entertaining aspect of such a book are the salty comments of the editors, which may range from criticisms to very brief essays. They vary from satire to surprise.

WILLIAM B. BEAN, M.D.

Some Milestones in the History of Hematology. By Camille Dreyfus, M.D. Price, $4.50. Pp. 87, with illustrations. Grune & Stratton, Inc., 381 Fourth Ave., New York 16, 1957.

Dreyfus has gathered together a series of items in the history of hematology, with conspicuous emphasis on contributions of French hematologists. Since this is a selective work, the author is certainly at liberty to pick out those he wants to write about. The writing is delightful, and the short historical sketches are very illuminating. The latter portion of the book is taken over with a charming biographical sketch of Georges Hayem. This book will appeal not only to hematologists but to internists and anyone interested in the history of medicine. The sketches are excellent, but certainly it is not a systematic treatise. A reflection which comes from reading this book is that from the time of Leeuwenhoek to Hayem for two-hundred years microscopy did not deign to seek out medicine. Within the realm of medical practice certain systems, threatened by facts,

rejected the microscope as a means to extend the clinical examination. Reserved for botanists and entomologists, microscopy came to hematology relatively late.

WILLIAM B. BEAN, M.D.

Since 1845: A History of the Mutual Benefit Life Insurance Company. By Mildred F. Stone. Price, $4.50. Pp. 236, with illustrations. Rutgers University Press, New Brunswick, N. J., 1957.

The connections of medicine and life insurance are many and important, though the average physician does not pay too much attention to them. This interesting history of an outstanding life insurance company gives an excellent synoptical view of the changing pattern of life insurance as well as medical knowledge reflecting changes in our culture and in our history. A number of points of medical interest may be indicated by the following facts from this book. Use of information about blood pressure was begun in 1911, and only the systolic reading was used. It was required only for applicants over the age of forty who were getting larger policies. About the same time routine urinalysis became part of the general evaluation of applicants for life insurance. The whole story of disability insurance, its waxing and waning, its abuses and its accomplishments, is told very clearly, with emphasis now on rehabilitation. Those who remember the days of depression well will not be surprised that many and large claims in suicide cases reached their peak in 1932, when suicides accounted for six per cent of the company's claims. The role of heart disease and declining role of infections are well known as factors of importance today. The problem of automobile risks and aviation are outlined in their impact on insurance. Many actuarial mysteries are clarified for the lay reader. The present all-out interest in research, the efforts at understanding the new socioeconomic problems of an aging society, and the numerous interconnections of preventive medicine, public health, the actuarial sciences, and research into the various processes and mechanisms of disease are all interwoven in a story which is full of many historical allusions which few people not concerned in the business would think of as having profound importance for life insurance. As an example of the interconnections of various aspects of medicine and life insurance for the last one hundred ten years this book has much of interest to a physician.

WILLIAM B. BEAN, M.D.

Gynecological Operations. By Heinrich Martius. Translated and edited by Milton L. McCall, M.D., and Karl A. Bolten, M.D. Price, $20. Pp. 397, with 450 illustrations. Little, Brown & Company, 34 Beacon St., Boston 6, 1957.

The seventh edition of "Gynecological Operations," by Prof. Heinrich Martius, is the latest and best edition of what has become the preeminent continental work of pelvic surgery in women. The first English translation appeared in 1939 under the editorial supervision of the late W. A. Newman Dorland.

The present translation, under the editorship of Dr. Milton L. McCall and Dr. Karl A. Bolten, presents all the valuable features of the older work as well as a large amount of new material. The book presents chapters describing all the common gynecological operations.

Each operation is described in a step-by-step detail, and in addition there are excellent illustrations depiciting the important features of each operative procedure. One important feature is that the topographic anatomy and relationship are beautifully illustrated. In addition there are chapters concerning abdominal incisions, herniotomies, and intestinal operations. This type of material is usually omitted from most textbooks on gynecological surgery.

This book fulfills a real need for information of this type, and without question one of the most important features is the excellent illustrations. A book of this type will be of particular interest to the resident in obstetrics and gynecology, the trained gynecologist, and the general surgeon called upon to do pelvic surgery. The book will be of limited value to the average internist, but the anatomical reviews and descriptive material concerning pelvic pathology will be of value.

W. C. KEETTEL, M.D.

Ciba Collection of Medical Illustrations: Volume 3: A Compilation of Paintings on the Normal and Pathologic Anatomy of the Digestive System. Part III: Liver, Biliary Tract and Pancreas. By Frank H. Netter, M.D., with a board of contributors and consultants. Price $10.50. Pp. 165, with 133 illustrations. Publications Department, Ciba Pharmaceutical Products, Inc., 556 Morris Ave., Summit, N. J., 1957.

For better or worse we are in an era in which a major portion of postgraduate medical education is carried on by the drug houses. The pabulum offered by them to American physicians runs the gamut of the often confused and clumsy efforts of the detail men through advertising publications containing all kinds of pseudoscientific and scientific educational bits, plus sales appeal, to movies, to reports of conferences of experts on various medical subjects brought together by the biologic firms, and finally to first-rate medical textbooks prepared by physicians and teachers of solid scientific accomplishment. This third volume prepared under the auspices of the Ciba company belongs in the latter category.

Like the preceding volumes of medical illustrations of the nervous system and reproductive system, this book on the liver, biliary tract, and pancreas is a superb piece of workmanship. Every page contains striking colored drawings by Frank Netter, filling half the space, in which the points are amplified by simple diagrams. The other half of the page is filled with printed material discussing the illustration. Regardless of whether one regards as good or bad this glorification of the illustration as the principal medium of informing the reader rather than making it the modest handmaiden of the printed word, he must admit that it is effective.

After delineating the normal anatomy of the liver, bile ducts, and pancreas, the physiology and pathologic physiology and liver-function tests are dealt with, after which the diseases of the various organs are illustrated in detail. As might be expected, there is often oversimplification, and while a fairly extensive bibliography is given for each section it is not referred to in the text. There is no discussion of treatment.

The pictures and discussions were prepared under the supervision of Oscar Bodansky, Eugene Cliffton, Donald D. Kezoll, Hans Popper, and Victor M. Sborov—all of whom have had extensive experience with the type of portrayal of the physiology and abnormalities of the organs with which this volume is concerned. One has laid before him in a clear and graphic but summarized manner the modern concepts backed by these men of authority. But the book must not be regarded in any sense as a complete text, and indeed the authors had no such intention.

In the introduction it is stated that the volume is sold at cost. When one contemplates this nine by twelve inch book with 133 magnificent full-color plates he wonders how the expense was kept low enough to sell the book for $10.50. The Ciba people are to be congratulated on this important contribution to medical education.

PAUL S. RHOADS, M.D.

A Summary of the Iowa Breakfast Studies. Price, not given. Pp. 50, with 16 figures. Cereal Institute, Inc., 135 S. LaSalle St., Chicago 3, 1957.

This volume summarizes and interprets twenty scientific articles published between 1949 and 1956. K. Daum and W. W. Tuttle, of the departments of nutrition and physiology of the State University of Iowa College of Medicine, were the principal investigators.

Fifty-four male subjects, aged twelve to eighty-three years, and sixteen women, aged eighteen to twenty-seven years, participated in a series of physiological tests designed to measure work capacity in the late morning hours. Studies of the blood sugar and the utilization of protein, certain minerals, and vitamins were done with twenty-three subjects. The principal variables were no breakfast, coffee only, and two "basic" breakfasts providing twenty-five grams of protein and seven hundred fifty Calories each. One "basic" breakfast was lactovegetarian; the other included bacon and eggs. Except for the twenty-three subjects on balance studies, the diet, other than breakfast, was not controlled. A limited test of the blood sugar in the late morning hours was made after breakfasts containing ten, fifteen, and twenty-five grams of protein and of work capacity after a breakfast of twenty-five grams of protein derived from plant sources only. Each subject served as his own control.

The original papers were technically sound and carefully reported. Average work capacity was more variable in the late morning without breakfast or with coffee only than with either of the "basic" breakfasts or the breakfast containing only plant protein. There was

no difference in the response of subjects on either of the breakfasts containing twenty-five grams of protein and seven hundred fifty Calories. There were individual subjects in each group who performed equally well with or without breakfast. However, the generalization that "it had been proven that an adequate breakfast should contain one-fourth the total daily caloric requirement" may be questioned, since no studies were done on intermediate caloric intakes, and the limited data presented on breakfasts containing fifteen grams of protein suggest that a lower protein intake may be quite as satisfactory as that in the arbitrarily defined "basic" breakfasts. The assumptions of the authors of this publication concerning bedtime snacks of milk and cereal may be true, but they were not tested in this series of experiments.

Many incidental data on oxygen consumption and specific dynamic action are recorded which are useful, since few studies have been done after the ingestion of mixed meals. The results of the balance experiments were valuable in that little difference in the efficiency of utilization of nutrients was found in male subjcts from twelve to eighty-three years of age.

MARGARET OHLSON, Ph.D.

Mesenchymal Diseases in Childhood. Report of the Twenty-Second Ross Pediatric Research Conference. Edited by S. J. Fomon, W. O. Robertson, and J. E. Jeffries. Price not given. Pp. 104, with 25 illustrations. Ross Laboratories, Columbus 16, Ohio, 1957.

This small paper-bound volume reports papers presented at a symposium on mesenchymal disease in childhood, conducted under the auspices of the Department of Pediatrics of the University of Utah College of Medicine, in October, 1956. The participants were well chosen for their respective topics. Each of the topics is concise and presents a summation of the present state of knowledge together with working hypotheses of research in that field. The main topics are general considerations in mesenchymal diseases, biochemical and hematological alterations in mesenchymal diseases, hormonal alterations in mesenchymal diseases, and clinical aspects of mesenchymal diseases. Under each major heading there are from three to six subtopics which are well presented and which cover the subject concisely but adequately. The discussions on juvenile rheumatoid arthritis, on systemic lupus erythematosus, and on renal diseases in children are of particular excellence. This small volume is highly recommended to those persons who are working in the investigative fields relating to any of these mesenchymal disorders. It is well edited and contains a surprising amount of valuable material.

ROBERT E. HODGES, M.D.

Physiology of Prematurity. Edited by Jonathan T. Lanman. Price, $3.25. Pp. 151, with 42 illustrations. Josiah Macy, Jr. Foundation, 16 W. 46th St., New York 36, 1957.

This is the first of a series of conferences to explore problems associated with premature birth. The first section of the book is devoted to the general topic of fetal-maternal endocrinology in late pregnancy. The large size of the adrenal in the fetus led to considerable speculation as to its physiological significance. Does chorionic gonadotropin stimulate the fetal cortex early in gestation? Does the small adrenal of the anencephalic monster indicate a failure of pituitary corticotropin in the last trimester? What is the relative responsiveness of the newborn adrenal to corticotropin? Is hypoxia a stimulus for adrenal enlargement? Does adrenal growth decline with a shift from fetal to adult hemoglobin? Androgens can be extracted from fetal adrenal tissue, but whether they are released into the fetal circulation is not known. The defective steroid biosynthesis giving rise to the adrenogenital syndrome was mentioned. There were then some comments on uterine contraction patterns in late pregnancy. These transient speculations may ultimately stimulate some of the participants to determine whether any of these hormonal factors contribute to the sixty-eight per cent of premature deliveries for which there is no obvious cause.

The second portion of the conference considered the general topic of fetal and placental circulation in late pregnancy. Much of the factual information was from Dr. Dawes' observations in fetal sheep. These were delivered by cesarean section, and while the placenta was still attached a series of intravascular catheters were passed to determine oxygen saturation and blood flow in various parts of the body. This led to questions and comments on the blood flow in the fetal heart and its deviations in atrial and septal defects. The question of blood flow in the collapsed and the distended lung was argued. There were

passing comments on the flow of blood through the placental sinuses and the influence of uterine contractions on this rate of flow. None of these aspects of circulation were considered in specific relation to a premature infant or a premature labor. Probably this was deliberate, since the introductory remarks state, "Our hope, in arranging this conference, was to go as far afield as possible, even to the inclusion of men whose work comes no nearer to premature infants than, perhaps, fish, or worms, or even botany."

J. T. Bradbury, M.D.

Heart Sounds, Cardiac Pulsations, and Coronary Disease. By William Dock, M.D. Price, $2.50. Pp. 98, with 23 illustrations. University of Kansas Press, Lawrence, Kan. 1956.

Bill Dock is in the tradition of the memorable peripatetic professors of the ninteenth century in American medicine, and his wanderlust in moving about from place to place reflects his restless spirit in medical research. He has become a very useful gadfly, deflating the pompous and inspiring a proper regard for inquiry in younger investigators and clinicians. The three lectures which constitute Series 21 of the Porter Lectures from the University of Kansas are good up-to-date résumés of three fields of active investigation in cardiology to which the author himself has made notable contributions. Not the least of the value of these essays is their close connection with the current of medical history, the many devious meanderings of which are illustrated in a delightful and breezy style by appropriate references and commentaries. Many dramatic examples of what Wilfred Trotter has so well called the mysterious viability of the false are discussed in the book. Unhappily, Bill Dock can give us no very hopeful clues for bringing this trend to a halt, though he shows by precept and example and in a style that is like a refreshing breeze on a hot summer day how fruitfully the intellect may be employed in tackling and solving medical problems of a high order of complexity and what fun it can be. This book should be in all medical libraries and will please those who savor their medical reading rare and well done at the same time.

William B. Bean, M.D.

Atlas of Clinical Endocrinology. By H. Lisser, M.D., and Wilberto F. Escamilla, M.D. Price, $18.75. Pp. 476, with 148 illustrations. The C. V. Mosby Company, 3207 Washington Blvd., St. Louis 3, 1957.

The authors of this atlas are to be congratulated on compiling a clinical atlas of endocrinology which incorporates a large number of photographs in conjunction with a concise and highly readable description of endocrine disorders. In most instances the salient features of differential diagnosis are so clearly demonstrated as to leave little doubt in the reader's mind. The subject material is standard for any textbook of endocrinology in that it begins with disease of the pituitary and progresses through those of the thyroid gland, the parathyroids, the adrenals, the pancreas, the testes, and the ovaries and ends with miscellaneous syndromes. The clinical acumen of the authors is clearly reflected in the quality of their presentation. It would be surprising, indeed, if some areas of disagreement did not exist, but these are few and of minor importance when considered in the light of the vast amount of material presented. The book is handsomely bound and printed on a high grade of paper. The photographic reproductions are excellent. There are sixty-three short chapters, each of which deals with a clinical condition or syndrome, with the exception of Chapter 31, which deals with x-ray procedures. This would seem to be a minor editorial error and does not detract from the value of the book. I would highly recommend this volume to clinicians who are interested in clinical endocrinology, as it provides a rapid and comprehensive source of reference to any major topic in this field, including a satisfactory bibilography.

Robert E. Hodges, M.D.

Clinical Proctology. By J. Peerman Nesselrod, B.S., M.S., M.Sc. (Med.), M.D., F.A.C.S., F.A.P.S. Price, $7. Pp. 296, with 72 illustrations. W. B. Saunders Company, 218 W. Washington Sq., Philadelphia 5; 7 Grape St., Shaftsbury Ave., London, W. C. 2, 1957.

The author's stated aims were to provide in written form the part of his experience useful to the general practitioner, to correlate the basis science studies and clinical work of medical students and house staff, to provide a detailed discussion of proctoscopy of use to the general practitioner and internist, and to provide an incentive for the general surgeon

to bring his results in anorectal surgery to the same creditable plane achieved in other fields of surgery. The first chapter of "Clinical Proctology" is a thoughtful thorough discussion of anal and rectal anatomy and physiology. The discussion of diagnostic procedures gives useful information concerning technique, equipment used, and the findings of proctoscopy. The separate chapters concerned with the diagnosis and treatment of hemorrhoids, fissure, abscess and fistula, contracture, and preoperative and postoperative care of these patients are based on the thesis that infection is the principal and always underlying cause of these disorders. Short chapters, discussions not intended to be and not complete, of rectal prolapse, anorectal malformations, the proctoscopic findings in a miscellaneous group of colon disorders, neoplastic diseases, and anal pruritus are included. The final chapter provides practical suggestions concerning enemas, laxatives, suppositories, anal warts, pilonidal disease, etc. The author's recommendations are in accordance with current practice, and the operative techniques described are sound. Many areas of the book will be elementary to the general practitioner, house officer, internist, and general surgeon. The text tends to be wordy, sometimes needlessly repetitious, and occasionally ambiguous. It is doubtful whether prolonged detailed discussions of operative techniques will prove useful to many, if any, readers. An apparent omission was the failure to advise use of carbon dioxide with electrosurgery of the rectum and colon. The brief bibliography is heavily weighted with the author's colleagues and fails to give due credit to contributions made in this field by British authors. A number of the illustrations were not clear to me. The degree to which "Clinical Proctology" accomplishes the author's aims will, of course, be dependent upon the reader. However, the monograph should prove of greatest interest to medical students and interns. There is doubt whether many general surgeons will accept with equanimity the author's premise in their behalf and thus accomplish his last objective.

JOSEPH A. BUCKWALTER, M.D.

News and Comment

ANNOUNCEMENTS

Fourth International Conference of Goiter.—The London Thyroid Club and the American Goiter Association announce that the Fourth International Conference on Goiter will be held in London, England, in 1960. Scientific sessions will be held in the Royal College of Surgeons on July 6, 7, and 8, 1960

Those who desire to submit abstracts of papers for consideration of appearing on the program should write to Selwyn Taylor, F.R.C.S., 3 Roedean Crescent, Roehampton, London S. W. 15, England or John C. McClintock, M.D., 149½ Washington Ave., Albany 10, N. Y.

Travel and hotel accommodations may be secured from Thomas Cook and Sons, Ltd.

A very few Honoraria will be available for travel assistance. For further particulars contact either of the above.

Van Meter Prize Award.—The American Goiter Association again offers the Van Meter Prize Award of $300 and two honorable mentions for the best essays-submitted concerning original work on problems related to the thyroid gland. The award will be made at the annual meeting of the Association, which will be held in the St. Francis Hotel, San Francisco, June 17, 18, and 19, 1958, providing essays of sufficient merit are presented in competition.

The competing essays may cover either clinical or research investigations, should not exceed 3000 words in length, and must be presented in English. Duplicate typewritten copies, double spaced, should be sent to the Secretary, Dr. John C. McClintock, 149½ Washington Ave., Albany 10, N. Y., not later than Feb. 1, 1958. The committee who will review the manuscripts is composed of men well qualified to judge the merits of the competing essays.

A place will be reserved on the program of the annual meeting for the presentation of the winning essay by the author if it is possible for him to attend.

Meeting of Western Society for Clinical Research.—The 11th annual meeting of the Western Society for Clinical Research will be held Thursday afternoon, Friday morning, and Saturday morning, Jan. 30 through Feb. 1, 1958, at Carmel-by-the-Sea, Calif.

Information regarding the meeting may be obtained from Arthur J. Seaman, M.D., Secretary-Treasurer, Western Society for Clinical Research, University of Oregon Medical School, Portland 1, Ore.

Public Health Service Bulletin on Diseases of Blood Vessels of the Brain.—The Public Health Service has released a new illustrated publication on disease of blood vessels of the brain, third ranking cause of death in the United States.

Strokes and other effects of cerebral vascular disease caused an estimated 179,110 deaths in 1956. Approximately 2,000,000 people are incapacitated or handicapped by brain blood vessel disease, the booklet states.

Dr. James Watt, Director of the National Heart Institute of the Public Health Service, which prepared the publication, said that many persons suffering from cerebral vascular disease can be restored to near-normal lives.

"Strokes have been too greatly feared and misunderstood," he said. "The booklet encourages a hopeful, constructive attitude by presenting simple understandable facts about cerebral vascular disease, its causes and effects, and what can be done about it. With proper care and treatment, 9 out of 10 of its victims can be taught to walk again and 3 out of 10 can be restored to gainful work."

The booklet shows the five important ways in which diseases impair the working of the brain and outlines steps involved in treatment and rehabilitation.

"Cerebral Vascular Disease and Strokes" is Public Health Service Publication Number 513. A free copy may be obtained from the Heart Information Center, National Heart Institute, Bethesda 14, Md.

SOCIETY NEWS

Fifth International Congress of Internal Medicine.—Over 1600 American physicians have joined the International Society of Internal Medicine during the past two months. This equals the number from all the other countries of the world. Thus, with continuing accessions, more than 3000 will be eligible to attend the Fifth Congress at Philadelphia, April 23-26, 1958. It is anticipated that at least 1000 American and 400 overseas physicians will be present. Many of the foreign visitors will also attend the Annual Session of the American College of Physicians, at Atlantic City, N. J., and the subsequent meetings of the Society of Clinical Investigation and the Association of American Physicians, also at Atlantic City. Some will stay over for the World Gastroenterological Congress and the annual meeting of the American Gastroenterological Association in Washington, D. C., May 24-31. Tours of medical and scientific centers in the Far West, Midwest, and along the eastern sea coast will also be available.

Among the participants on the scientific program from other countries will be Prof. Nanna Svartz, of the Karolinska Hospital, Stockholm, Sweden, who was one of the founders of the International Society; Sir Russell Brain, President of the Society and of the Royal College of Physicians of London; Dr. C. deLangen, Holland; Prof. C. Jimenez-Diaz, Spain; Prof. A. L. Miasnikov, Russia; Prof. R. M. Castex, Argentina; Dr. Otto Wegelius, Finland; Prof. A. Floros, Greece, and many other distinguished physicians. Among the outstanding North American contributors to the program will be Dr. Charles H. Best, Professor of Physiology at the University of Toronto, co-discoverer of insulin; Dr. Philip S. Hench, of the Mayo Clinic, Rochester, Minn., Nobel Prize winner and past-president of the Arthritis and Rheumatism Foundation; Dr. Howard A. Rusk, Professor of Physical Medicine and Rehabilitation, New York University Bellevue Medical Center; Dr. Shields Warren, Professor of Pathology, Harvard Medical School, Boston, Member of the Medical Advisory Committee and formerly Director of Biology and Medicine of the Atomic Energy Commission, and Dr. Irving S. Wright, Clinical Professor of Medicine, Cornell University School of Medicine, New York, past-president of the American Heart Association.

Entertainment features will include a reception at the Sheraton Hotel, a concert by the Philadelphia Orchestra, a banquet, and a luncheon at the University of Pennsylvania Museum. For the ladies there will be, in addition, a luncheon at the Philadelphia Museum of Art and a tour to the du Pont Gardens. Also, for the foreigners, dinners in private homes will be arranged for one evening.

The Executive Committee of the International Society of Internal Medicine includes as President, Sr. Russell Brain, London, England; as Secretary, Prof. H. Ludwig, Basel, Switzerland; as Treasurer, Dr. E. Jacottet, Basel, Switzerland; also Sir Harold Boldero, London, England; Prof. A. Gigon, Basel, Switzerland; Prof. C. Jimenez-Diaz, Madrid, Spain; Prof. L. Justin-Besancon, Paris, France; Dr. T. Grier Miller, Philadelphia, and Prof. N. Svartz, Stockholm, Sweden.

Dr. T. Grier Miller, President of the Fifth International Congress, has recently named the following as chairmen and chairwoman of the local arrangements committees: Symphony Concert Committee, Dr. Alexander Rush; Special Entertainment Committee, Dr. Harrison F. Flippin; Banquet Committee, Dr. David A. Cooper; Registration Committee, Dr. Leandro M. Tocantins; Women's Entertainment Committee, Dr. Elizabeth K. Rose; Transportation Committee, Dr. Truman G. Schnabel Sr.

Dr. Edward L. Bortz, former President of the American Medical Association, will serve as official representative of the Fifth International meeting of the College of Physicians and Surgeons of South Africa, Sept. 16-21, 1957. Dr. Bortz will also be the official Delegate of the American College of Physicians to the South African Congress. He, together with Sir Russell Brain, will seek to promote among those attending the meeting at Durban an interest in participation in the Fifth International Congress.

Dr. Leandro M. Tocantins, Chairman of the Registration Committee of the Congress, will serve in a similar capacity when he visits Brazil and Argentina from Aug. 23 to Sept. 7, 1957. He will meet with Pan-American representatives on the occasion of the celebration of the 10th anniversary of the founding of the Hospital Dos Servidores Do Estado, Rio de Janeiro, Brazil.

Although additional funds are needed to cover administration costs, transportation services, publications, and other general expenses, many generous contributions have already been

received. The present sponsors include the American College of Physicians, the National Institutes of Health, the National Foundation of Infantile Paralysis, and the Albert and Mary Lasker Foundation. Also, donations have been received from Burroughs Wellcome & Company, Inc., Hoffman-La Roche, Inc.; Johnson & Johnson; Eli Lilly and Company, the Merrell National Overseas Laboratories; Prize Laboratories; G. D. Searle & Co.; Smith, Kline & French Foundation; The Upjohn Company, and the A. H. Robins Company, Inc.

Those physicians in North and South America who wish to become members of the International Society of Internal Medicine and to attend the Fifth International Congress of Internal Medicine should request application forms from Mr. E. R. Loveland, Secretary-General of the Fifth Congress, 4200 Pine St., Philadelphia 4. Dues are $5 for a two-year period. Physicians in other countries should write to Prof. H. Ludwig, 2, Med. Aberlung Burguspital, Basel, Switzerland.

Anyone who wishes to participate in the program should send the title of his paper and a 200-word abstract, in triplicate, to Dr. Frank N. Allan, 605 Commonwealth Ave., Boston 15.

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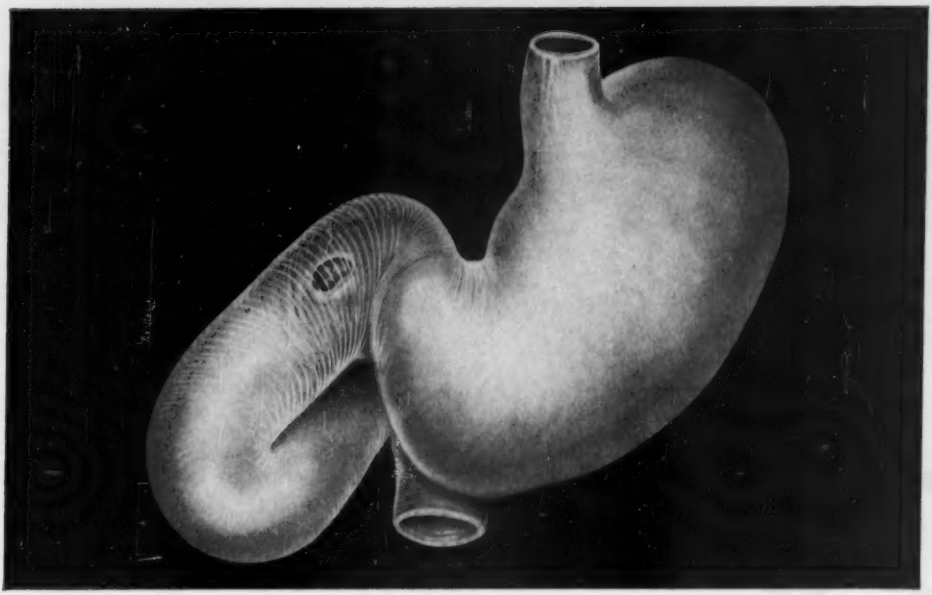

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*Lichstein, J.; Morehouse, M. G., and Osmon, K. L.: Pro-Banthine in the Treatment of Peptic Ulcer. A Clinical Evaluation with Gastric Secretory, Motility and Gastroscopic Studies. Report of 60 Cases, Am. J. M. Sc. *232*:156 (Aug.) 1956.

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(1) Asung, C. L.; Charcowa, A. I., and Villa, A. P.: Sea View Hosp. Bull. *16*:80, 1956. (2) Asung, C. L.; Charcowa, A. I., and Villa, A. P.: New York J. Med. *57*:1911 (June 1) 1957. (3) Report on Field Screening of Nostyn by 99 Physicians in 1,000 Patients, June, 1956.

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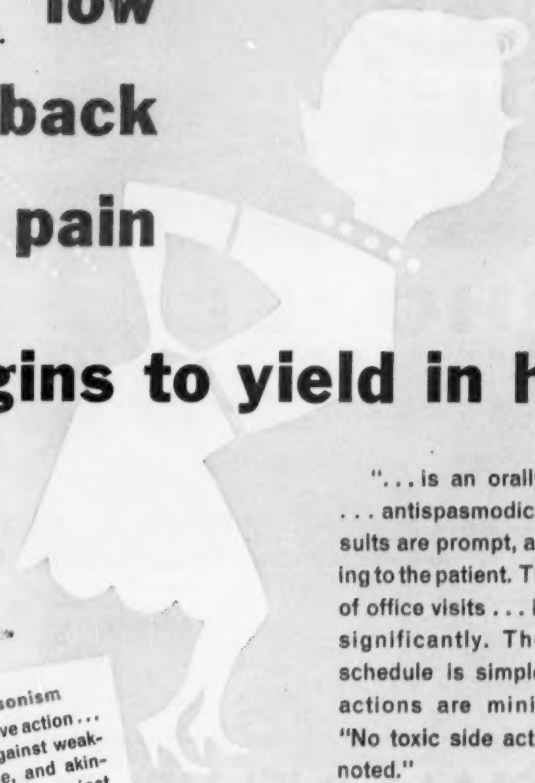

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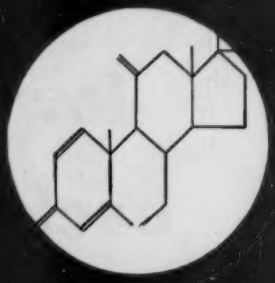

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1 Bollet, A.J., Black, R., and Bunim, J.J.: J.A.M.A. *158*:459 (June 11) 1955.

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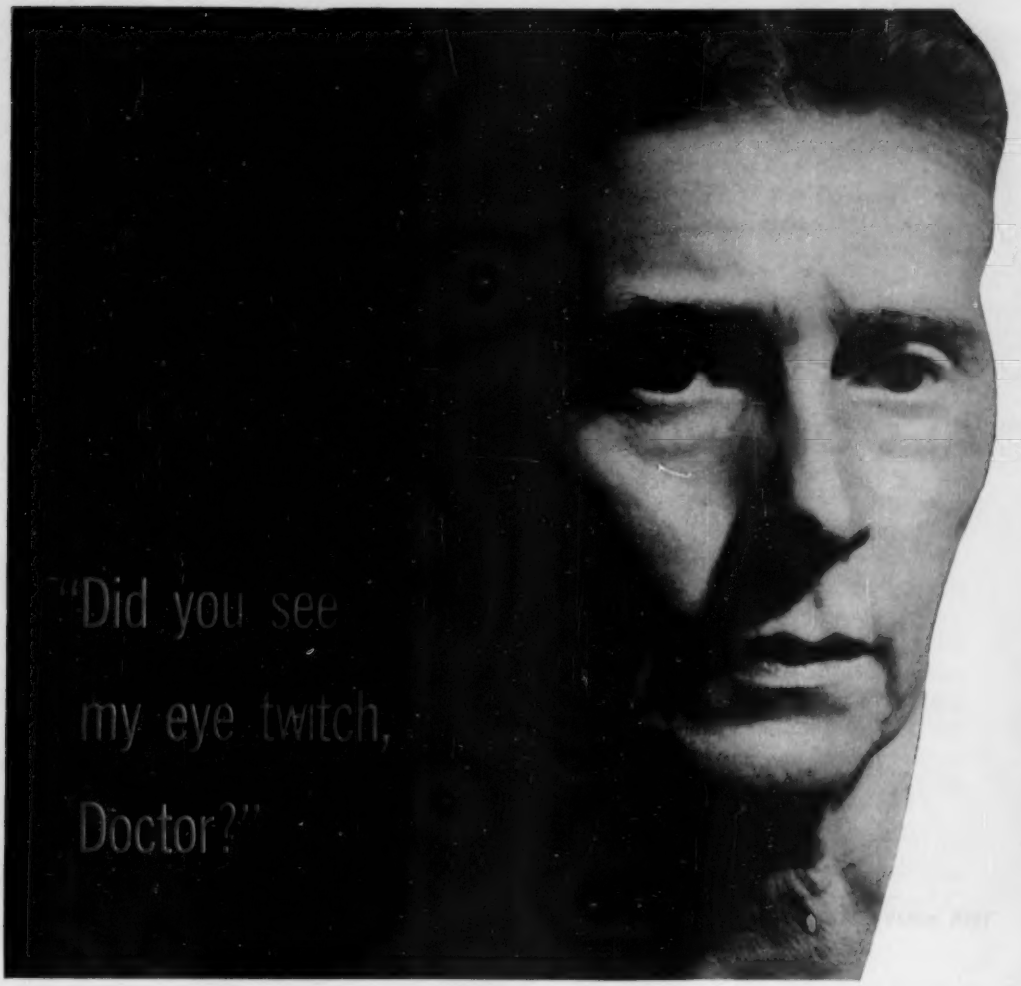

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1. *Nussbaum, H. E., Leff, W. A., Mattia, V. D., Jr. and Hillman, E.: An effective combination in the treatment of the hypertensive patient. Am. J. M. Sc.* **234**:150, *Aug. 1957.*

2. *Dunsmore, R. A., Dunsmore, L. D., Bickford, A. F. and Goldman, A.: Meprobamate as adjuvant therapy in hypertension: A preliminary report. Am. J. M. Sc.* **233**:280, *March 1957.*

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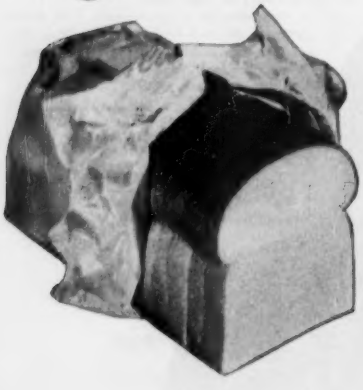

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* Smith, Jr., A.: *J.A.M.A.*, 152:384, May 30, 1953. Brown, W. T., and Smith, J. A.: *South. Med. Jour.*, 46:582, June, 1953. Smith, J. A.: *Postgrad. Med.*, 16:316, Oct., 1954. McCullagh, W. H.: *Jour. Florida Med. Assn.*, 41:718, Mar., 1955.

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